

Protocol #: LCI-HEM-MYE-CRD-002

TITLE: Phase II Study of Carfilzomib, Lenalidomide, Dexamethasone and Elotuzumab in Relapsed/Refractory Multiple Myeloma

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PROTOCOL SIGNATURE PAGE
Phase II Study of Carfilzomib, Lenalidomide, Dexamethasone and Elotuzumab in
Relapsed/Refractory Multiple Myeloma

The signature below constitutes the approval of this protocol and the attachments, and, provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Signature of Sponsor-Investigator

Date

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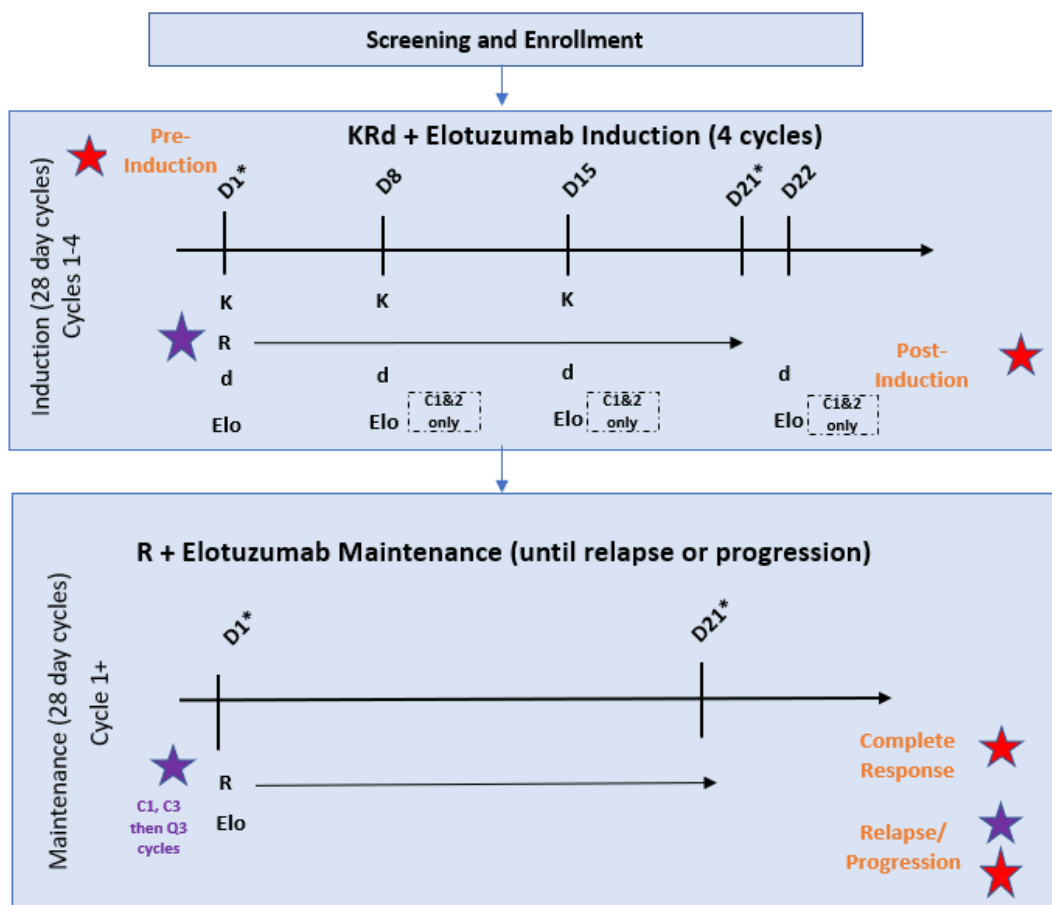
SYNOPSIS

TITLE	Phase II Study of Carfilzomib, Lenalidomide, Dexamethasone and Elotuzumab in Relapsed/Refractory Multiple Myeloma
STUDY POPULATION	Relapsed or Refractory Multiple Myeloma
PHASE	II
SUMMARY OF STUDY RATIONALE	<p>Elotuzumab (BMS-901608, HuLuc63) is a first-in-class, immunostimulatory, humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7, also called CS1), a glycoprotein highly expressed on myeloma cells independent of cytogenetic abnormalities. Elotuzumab is approved for the treatment of previously treated MM in combination with lenalidomide and dexamethasone (Rd). The regimen of carfilzomib (a proteasome inhibitor) with Rd (KRd) is a highly active regimen used in the treatment of relapsed and/or refractory MM. The immunomodulatory effects of KRd have a strong potential for synergy with those of elotuzumab, and data from elotuzumab in combination with the proteasome inhibitor bortezomib support the safety of combining elotuzumab with KRd.</p>
STUDY DESIGN	<p>This single arm, open-label phase II study is designed with the primary objective of evaluating the efficacy of induction therapy comprised of 4 cycles of carfilzomib, lenalidomide, dexamethasone and elotuzumab (KRd+elotuzumab) in terms of very good partial response or better (VGPR+) in subjects with relapsed and/or refractory MM, and comparing to relevant historical controls. Post induction, all subjects will undergo disease evaluation for assessment of the primary endpoint. Maintenance therapy comprised of elotuzumab and lenalidomide (R+elotuzumab) will start directly after induction and continue until relapse or progression.</p>
OBJECTIVES	<p><u>Primary Objective:</u> The primary objective is to evaluate the efficacy of elotuzumab when combined with KRd in terms of very good partial response or better (VGPR+) to induction therapy in subjects with relapsed or refractory multiple myeloma, and compare to relevant historical controls. Response will be assessed based on the International Myeloma Working Group (IMWG) 2016 criteria.</p> <p><u>Secondary Objectives:</u> Secondary objectives include evaluation of elotuzumab in combination with KRd by estimating the following:</p> <ul style="list-style-type: none"> • Overall response rate (ORR) defined as the percent of subjects achieving a partial response or better per IMWG 2016 criteria. • Progression-free survival (PFS) defined as the time from treatment start (Cycle 1, Day 1) until disease progression or death. • Overall survival (OS) defined as the time from treatment start until death.

	<ul style="list-style-type: none"> • Time to disease progression (TTP) defined as the time from treatment start until disease progression. • Duration of response (DoR) in subjects achieving a partial response or better defined as the time from achieving a partial response until disease progression or death. • Time to next treatment (TTNT) as defined by the time from treatment start until the start of the first subsequent anti-cancer therapy after all protocol directed therapy is completed.
KEY INCLUSION CRITERIA	<ul style="list-style-type: none"> • Documented history of relapsed and/or refractory multiple myeloma per IMWG 2016 criteria [22] (biochemical and/or clinical relapse per IMWG criteria) (subjects refractory to bortezomib and/or lenalidomide are eligible; subjects who previously received carfilzomib are eligible provided they experienced a response and relapsed >60 days after completion of treatment) • Prior treatment with one line (and no more than one line) of systemic therapy for MM • Age ≥ 18 years • ECOG ≤ 2 • Measurable disease: <ul style="list-style-type: none"> ○ Serum M-protein ≥ 0.5 g/dL OR ○ Urine M-protein ≥ 200 mg/24 h OR ○ Involved free light chain (FLC) level ≥ 10 mg/dL provided serum FLC ratio is abnormal • Recovered from any prior treatment-induced toxicities to \leq grade 1 or baseline • Adequate organ and bone marrow function • Negative serum pregnancy test in females of childbearing potential (FCBP) • Willingness to use required birth control as applicable
STATISTICAL CONSIDERATIONS	<p>The primary objective of this study is to evaluate the VGPR+ rate in subjects treated with elotuzumab in addition to the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed or refractory multiple myeloma subjects. This will be evaluated in terms of the percent of subjects who achieve a VGPR+ to induction therapy. Wang [6] reported a VGPR+ rate of approximately 40% in this patient population treated with KRd. This study will be used to test the null hypothesis that the VGPR+ rate in subjects treated with elotuzumab+KRd is less than or equal to 40%. Forty (40) response evaluable subjects will be enrolled, and if at least 21 of 40 subjects achieve a VGPR+, the null hypothesis will be rejected. The design will provide 90% power with a 1-sided alpha = 0.10 significance level, assuming the true VGPR+ rate is 60%. An improvement from 40% to 60% in the VGPR+ rate is considered clinically relevant.</p>

TOTAL NUMBER OF SUBJECTS	40
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SCHEMA



K: Carfilzomib
R: Lenalidomide
d: Dexamethasone
Elo: Elotuzumab

*R daily D1-D21(Induction and Maintenance)

Note: A bone marrow biopsy /aspirate will also be collected when confirming a complete response; bone marrow collection at relapse/progression is at the discretion of the investigator; during maintenance cycles 3+, peripheral blood will only be collected every 3 cycles(C5, C8, etc.)

★ Bone marrow aspirate/
biopsy for correlatives

★ Peripheral blood collection for correlatives

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1. BACKGROUND AND RATIONALE

1.1 Multiple Myeloma (MM)

Multiple myeloma (MM) is a neoplasm of plasma cells that is characterized by osteolytic bone lesions and organ damage, such as hypercalcemia, anemia, and renal insufficiency. Despite major advances in therapy, MM is still considered an incurable malignancy. The introduction of immunomodulatory agents (IMiDs; e.g., lenalidomide) and proteasome inhibitors (e.g., bortezomib, carfilzomib), coupled with advances in autologous stem cell transplant (ASCT) have improved progression free survival (PFS) and overall survival (OS) for MM patients. Unfortunately, the majority of patients still suffer relapses with progressively shorter disease free intervals with each relapse.

A number of doublet and triplet regimens are available to treat patients who progress or relapse after initial therapy, with choice depending on what the patient has already received, and their initial response. Those who relapse > 6 months after discontinuation of initial therapy may be re-treated with the same regimen. Common triplet regimens used for relapsed/refractory include bortezomib/lenalidomide/dexamethasone, and carfilzomib/lenalidomide/dexamethasone [1].

Carfilzomib is an epoxomicin derivative with the ability to irreversibly inhibit proteasomes. It has been shown in preclinical and early clinical studies to have activity in MM [2]. In addition, when measured against a broad panel of proteases including metallo, aspartyl, and serine proteases, carfilzomib demonstrated less reactivity against non-proteasomal proteases when compared to bortezomib [3]. Pre/post carfilzomib in vivo pharmacogenomics gene expression profiling data from the University of Arkansas Car-505 protocol (unpublished data) suggests that the use of carfilzomib may impact the more proliferative and high risk MM sub-clone in a given patient, whereas this effect was not seen with the proteasome inhibitor bortezomib [4]. The two agents share similar toxicity profiles, with intravenous bortezomib associated with a higher incidence of peripheral neuropathy.

1.2 Carfilzomib (Kyprolis®), Lenalidomide (Revlimid®), Dexamethasone (KRd) in Relapsed/Refractory MM

The combination of carfilzomib (Kyprolis®) with lenalidomide (Revlimid®) and dexamethasone (a regimen termed “KRd”) initially exhibited excellent clinical activity in a phase Ib/II clinical trial in relapsed/refractory MM patients. In the dose escalation portion of the study (n=40), no maximally tolerated dose (MTD) was identified, and the maximum planned dose (MPD; 27mg/m² of carfilzomib) was recommended for the phase II portion (with an initial dose of 20mg/m² on days 1 and 2 of cycle 1, with the overall dosing regimen defined as 20/27 mg/m²). The overall response rate (ORR) across the dose escalating cohorts was 62.5% [5]. In the phase II portion, 52 patients were enrolled and treated with the combination at the MPD for carfilzomib. The ORR in this cohort was 76.9% (the very good partial response or better [VGPR+] rate was 42.3%) and the median PFS was 15.4 months [6].

This trial was followed by the open-label phase III trial, ASPIRE, wherein KRd was compared to Rd in patients with relapsed/refractory MM (1-3 prior lines of therapy). Median PFS was significantly improved with the triplet (26.3 months compared to 17.6 months, $p=0.0001$), as was the VGPR+ rate (69.9% compared to 40.4%). Median OS was not yet reached at the time of the analysis, but the OS rate at 24 months favored the triplet (73.3% versus 65%, $p=0.04$). Notably, patients in the KRd arm reported better quality of life as compared to the Rd arm [7]. This trial led to the Food and Drug Administration (FDA) approval of carfilzomib in combination with Rd for the treatment of patients with relapsed or refractory MM.

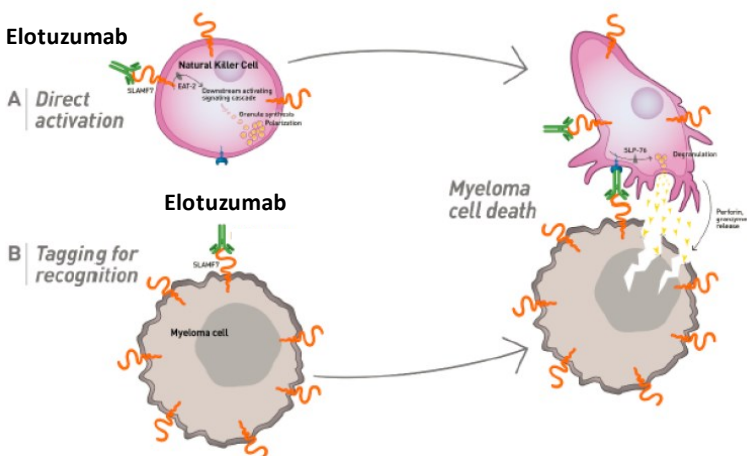
1.3 Elotuzumab

Elotuzumab (BMS-901608, HuLuc63) is a first-in-class, immunostimulatory, humanized immunoglobulin G1 (IgG1) monoclonal antibody (mAb) targeted against Signaling Lymphocyte Activation Molecule Family 7 (SLAMF7, also called CS1), a glycoprotein highly expressed on myeloma cells independent of cytogenetic abnormalities. Elotuzumab was approved by the FDA in November 2015 for the treatment of previously treated MM in combination with lenalidomide and dexamethasone (Rd). This approval was based on an open label phase III randomized trial (ELOQUENT-2) of Rd versus elotuzumab+Rd in relapsed or refractory MM patients who had received 1-3 prior therapies.

The function of the target of elotuzumab, SLAMF7, is not well characterized, but it appears to play a critical role in interactions between MM cells and the bone marrow stromal cells. SLAMF7 is also expressed on natural killer (NK) cells and at significantly lower levels on specific immune cell subsets [8]. SLAMF7 has not been detected on hematopoietic stem cells nor on other normal solid organ tissues [8].

Elotuzumab binding to SLAMF7 directly activates NK cells, but not myeloma cells. Elotuzumab bound to myeloma cells via SLAMF7 further activates NK cells via Fc receptors, thereby enabling selective killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC) with minimal effects on normal tissue [9]. This dual mechanism of action (direct NK cell activation and NK cell-mediated ADCC) is illustrated in Figure 1[8, 10].

Figure 1: Dual Mechanism of Action of Elotuzumab



1.3.1 Elotuzumab Preclinical Summary

Elotuzumab does not recognize nor bind to the SLAMF7 protein from species other than humans, and so the preclinical safety package was comprised of in vitro safety studies and in vivo biological evaluations. Elotuzumab (100 and 200 µg/mL) in vitro had no effect on lymphocytes, CD3, CD4, CD8 and B-cell counts in blood samples from healthy human donors. The NK cell counts were decreased on average by 20% at both doses of elotuzumab. Elotuzumab at concentrations up to 500 µg/mL did not adversely affect the ability of human bone marrow-derived hematopoietic stem cells to differentiate down the erythroid and myeloid pathways. Elotuzumab was also evaluated in a single-dose IV study in primates (rhesus monkeys) to explore for any potential off target effects. In this latter study, no elotuzumab-related effects were observed.

Safety pharmacology studies were not considered relevant in view of the specificity of the interaction of elotuzumab with its target. In particular, elotuzumab is targeting a molecule/pathway that is not known to be involved in the functioning of the 3 main organ systems: central nervous system, respiratory system, and cardiovascular system. This specificity is confirmed by the observed lack of cross-reactivity in various human tissues.

Experiments using an in vivo mouse xenograft model suggest that, while maximal antitumor activity is reached at elotuzumab serum levels of 70 to 430 µg/mL, minimal biological activity is seen at 2 to 13 µg/mL. In vitro experiments suggested that the elotuzumab concentration required to achieve saturation of SLAMF7 on peripheral blood mononuclear cells (PBMCs) from healthy donors was approximately 20 µg/mL.

In nonclinical models, elotuzumab plus bortezomib, lenalidomide, or pomalidomide had greater antitumor activity than either agent alone. Significant antibody-dependent killing of MM cells was observed when elotuzumab was incubated with L363 or OPM2 human MM cells in the presence of human PBMCs isolated from the blood of healthy donors or from the blood of MM subjects. No complement-dependent cytotoxicity was detected.

Elotuzumab treatment of mice bearing human xenograft MM tumors resulted in significant antitumor activity and eradication of tumors in many of the treated mice. See the latest version of the elotuzumab Investigator's Brochure (IB) for additional details.

1.3.2 Elotuzumab Pharmacodynamics

The relationship between SLAMF7 saturation on MM cells and elotuzumab levels in blood was assessed in 3 phase I studies. At doses of 10 and 20 mg/kg of elotuzumab, SLAMF7 receptors on bone marrow-derived myeloma cells were consistently saturated. See the latest version of the elotuzumab IB for additional details.

1.3.3 Elotuzumab Pharmacokinetics

The pharmacokinetics (PK) of elotuzumab was evaluated in over 600 patients who received the drug as monotherapy or in combination with other agents. Elotuzumab exhibits nonlinear PK, resulting in greater than proportional increases in area under the concentration-time curve (AUC) indicative of target-mediated clearance.

The multiple-dose PK of elotuzumab, given every week to every 4 weeks, was determined following IV administration of various doses. Increase in exposure was more than dose proportional from 0.5 to 20 mg/kg. Following weekly or every 2 weeks' administration of 10 mg/kg of elotuzumab in combination with lenalidomide/dexamethasone (Rd) or bortezomib/dexamethasone, mean trough concentrations (C_{min}) were above the target threshold concentration (70 mcg/mL) associated with maximal efficacy observed in the nonclinical xenograft human MM mouse model.

In the phase III trial combining elotuzumab with Rd (ELOQUENT-2), described in detail in Section 1.3.4.1), dosing elotuzumab weekly for the first 8 weeks of dosing followed by every 2-week dosing allows for attainment of steady-state exposure of elotuzumab approximately 6 weeks after the start of dosing. However, concentrations continued to rise for 3 more weeks. Once subjects were switched to every 2-week dosing, trough levels decreased to those reported at 6 weeks.

Clinically significant differences were not observed in the pharmacokinetics of elotuzumab based on age, gender, race, baseline LDH, albumin, renal impairment ranging from mild to end-stage renal disease (creatinine clearance less than 15 mL/min) with or without hemodialysis, and mild hepatic impairment (defined as total bilirubin \leq upper limit of normal (ULN) with AST $>$ ULN or total bilirubin 1.0 to 1.5 \times ULN, and any AST). The pharmacokinetics of elotuzumab in patients with moderate to severe hepatic impairment is unknown. The clearance of elotuzumab increased with increasing body weight supporting a weight-based dose. See the latest versions of the elotuzumab IB and prescribing information for additional details.

1.3.4 Elotuzumab Clinical Studies

As of the May 15, 2016 IB, 13 clinical studies sponsored by the manufacturer of elotuzumab (1 as monotherapy and 12 in combination with other agents) in subjects with

MM were either ongoing or complete. One additional trial of monotherapy has been conducted in high risk smoldering myeloma.

1.3.4.1 Combination with Lenalidomide and Dexamethasone

Elotuzumab in combination with lenalidomide and dexamethasone has been evaluated in a number of clinical trials, including the ELOQUENT-2 trial [11]. In ELOQUENT-2, elotuzumab was dosed at 10 mg/kg every week for the first two cycles (8 weeks) followed by elotuzumab 10 mg/kg every 2 weeks. Lenalidomide was dosed at 25 mg orally daily on days 1-21 of each cycle. Dexamethasone was given weekly throughout treatment. On the days of elotuzumab administration, 36 mg of dexamethasone was given [28 mg orally and 8 mg IV]. On the weeks elotuzumab was not administered (i.e., weeks 2 and 4 from cycle 3 on), subjects received 40 mg of oral dexamethasone.

The trial was designed with two co-primary endpoints: ORR (partial response [PR] or better using the European Group for Blood and Marrow Transplantation) and PFS. The median PFS and ORR were significantly improved in the elotuzumab arm (19.4 months and 79% [33% VGPR+]) as compared to the Rd (control) arm (14.9 months and 66%).

Serious adverse reactions were reported in 65.4% of patients treated on the elotuzumab arm and 56.5% of patients treated on the control arm. The most frequent serious adverse reactions (elotuzumab arm compared to the control arm) were: pneumonia (15.4% vs. 11%), pyrexia (6.9% vs. 4.7%), respiratory tract infection (3.1% vs. 1.3%), anemia (2.8% vs. 1.9%), pulmonary embolism (3.1% vs. 2.5%), and acute renal failure (2.5% vs. 1.9%). Adverse reactions occurring at a frequency of at least 20% (all grades) in the elotuzumab arm and that are 5% or higher in the elotuzumab arm compared to the Rd arm included: fatigue, diarrhea, pyrexia, constipation, cough, peripheral neuropathy, nasopharyngitis, upper respiratory tract infection, decreased appetite and pneumonia. Of note, the incidence of grade 3 or 4 fatigue was 12.6% in the elotuzumab arm vs. 11.7% in the Rd arm and the incidence of grade 3 or 4 pneumonia was 14.2% in the elotuzumab arm vs. 9.5% in the Rd arm. The rate of infusion related reactions (IRR) in the elotuzumab arm was 10% (n=33), with \leq grade 2 in the large majority (n=29). Seventy percent of the IRRs occurred within the first cycle. No patient experienced a $>$ grade 3 IRR [elotuzumab prescribing information and reference 11].

Laboratory abnormalities worsening from baseline with a frequency of at least 10% (all grades) in the elotuzumab arm and that are 5% or higher in the elotuzumab arm compared to the Rd arm included (grade 3 or 4): lymphopenia (76.7%); leukopenia (32.4%); thrombocytopenia (19.2%); hypoalbuminemia (3.9%); elevated alkaline phosphatase (1.3%); hyperglycemia (17%); hypocalcemia (11.3%); low bicarbonate (0.4%); and hyperkalemia (6.6%).

See the prescribing information and reference [11] for additional details on safety data from this trial. See the IB and Section **Error! Reference source not found.** for safety information across all clinical studies of elotuzumab to date. Section **Error! Reference source not found.** also summarizes the warnings associated with elotuzumab administration: infections, second primary malignancies, IRR and hepatotoxicity.

1.3.4.2 Combination with Bortezomib

Elotuzumab has been evaluated in combination with the proteasome inhibitor bortezomib in subjects with relapsed/refractory MM in a phase I [12] and subsequent randomized phase II study [13]. In the phase I trial, elotuzumab was administered from 2.5 to 20 mg/kg on days 1 and 11 of each 21-day cycle in combination with bortezomib (1.3 mg/m² IV on days 1, 4, 8 and 11). The phase I subjects, who had received a median of 2 prior therapies, did not experience any DLTs during cycle 1 of the maximum planned dose of elotuzumab of 20mg/kg. The most common \geq grade 3 adverse drug reactions were consistent with those reported previously for bortezomib and included lymphopenia (25%), fatigue (14%), and the following at 11% each (neutropenia, thrombocytopenia, peripheral neuropathy and hyperglycemia). Adverse reactions considered related to elotuzumab were primarily IRRs and resolved the same day of treatment. CS1 targets were saturated to a median of 80% at the 10 mg/kg dose of elotuzumab, and 95% at the 20 mg/kg dose, and serum concentrations of \geq 100 mcg/mL or greater at each of these doses was achieved [12].

In the randomized phase II trial, elotuzumab, bortezomib and dexamethasone (EBd), or bortezomib and dexamethasone (Bd), were administered in 3 week cycles for the first 8 cycles, followed by 4 week cycles until progression. Elotuzumab 10 mg/kg was administered weekly for cycles 1 and 2, on days 1 and 11 from cycles 3 to 8 and then every 2 weeks thereafter. Bortezomib 1.3 mg/m² IV was administered on days 1, 4, 8 and 11 for the first 8 cycles and days 1, 8 and 15 for all subsequent cycles. Dexamethasone was administered weekly as 20 mg orally on non-elotuzumab days or 8 mg orally plus 8 mg IV on days elotuzumab was also administered. The median PFS was longer in the triplet arm as compared to Bd, with minimal differences in adverse events between the two arms. The incidence of \geq grade 3 events were similar with the exception of infections (21% for the triplet versus 13% for Bd) and thrombocytopenia (9% for the triplet and 17% for Bd) [13].

1.4 Study Rationale and Design

Elotuzumab has demonstrated clinical efficacy in relapsed/refractory MM when combined with dexamethasone and lenalidomide [11] and has been shown to be safe and well tolerated when combined with the proteasome inhibitor bortezomib with or without dexamethasone [12, 13]. Further, the immunomodulatory effects of the KRd regimen, which incorporates the proteasome inhibitor carfilzomib, have a strong potential for synergy with those of elotuzumab (see Section 1.4.1).

Given this, we propose a phase II trial designed to evaluate the efficacy (rate of VGPR+) after 4 cycles of KRd+elotuzumab in subjects with relapsed/refractory MM. The VGPR+ rate will be compared to a historical control rate of 40%, with the aim of improving the rate to 60% with the addition of elotuzumab. The 40% historical control rate for KRd comes from the MPD cohort from the phase Ib/II trial [6]. This rate of 40%, which is lower than the rate from the ASPIRE trial [7], was selected as the historical control for several reasons. In the present study, we will be evaluating our primary endpoint after 4 cycles of therapy. While both the phase Ib/II trial and the ASPIRE trial reported the best response over the full course of therapy, in ASPIRE, KRd was given at a fixed schedule until

progression, with the majority of patients receiving more than 18 cycles of therapy. On the other hand, in the phase Ib/II study the frequency of carfilzomib dosing was reduced after 12 cycles from 6 times per month to 4, and the majority of patients received ≤ 12 cycles of therapy, making it more analogous to the present study. In addition, our trial includes subjects with light chain only disease, while these subjects were excluded from the ASPIRE study.

We have incorporated identical doses of carfilzomib and lenalidomide as were used in previous trials of KRd as induction [14-15], and have maintained the same weekly dose of dexamethasone when administered with elotuzumab as was used in the elotuzumab+Rd regimen described in Section 1.3.4.1. The elotuzumab dose of 10 mg/kg during induction is identical to the approved dose of this agent when combined with Rd and is the dose that was utilized in the randomized phase II trial of elotuzumab+Bd [13]. We are maintaining the frequency of weekly elotuzumab dosing during induction for the first 2 cycles. Post-induction, elotuzumab will be administered monthly in combination with lenalidomide, and dexamethasone will be omitted in an attempt to decrease long term toxicity. This is similar to an ongoing trial of elotuzumab in combination with lenalidomide as maintenance therapy after ASCT (NCT 02420860). Also similar to this latter trial, and to several other ongoing trials of elotuzumab in MM (NCT 02654132; 02612779; 02272803), the elotuzumab dose will be increased to 20 mg/kg as the frequency decreases to once monthly. Safety will be carefully monitored in this study, and toxicity data reviewed regularly at all study team meetings.

1.4.1 Correlatives

Beyond a direct anti-MM plasma cell (PC) activity, proteasome inhibitor/IMiD drug combinations such as KRd have a potent effect on immune effector cells and overall inflammation. Carfilzomib and lenalidomide in particular can activate NK cells and enhance NK cell-mediated lysis [16]. Bortezomib and lenalidomide have also been shown to promote Type 1 T helper (TH1) inflammation triggering T helper and cytotoxic T cells expansion [17]. Noticeably, dexamethasone can potentiate these strong pro-inflammatory stimuli by altering NK cell activating receptor expression [18] and sensitize T cells to anergy signaling [19].

The aforementioned mechanisms of immune modulation by KRd present strong potential synergy with elotuzumab. While plasma cells (including MM-PC) express high levels of SLAMF7 (CS1), NK cells and activated T cells share this receptor expression [20]. Elotuzumab enhances NK activation and myeloma cell killing through TH1 inflammation-dependent pathways [21].

In addition to exploring this synergy, correlative studies planned for this trial include evaluation of minimal residual disease (MRD). Relapse in MM, including in those who achieve a CR post treatment, is likely due to the presence of MRD undetectable by standard disease evaluation methods (i.e., assessment of monoclonal proteins in serum and urine and evaluation of bone marrow). MRD following therapy represents a state of immune equilibrium whereby detectable or undetectable low numbers of myeloma cells remain under surveillance as long as the immune environment continues to be

permissive, however after variable lengths of time, immune dormancy ends, leading to multiple myeloma progression.

In order to characterize KRd+elotuzumab synergistic activity on antitumor immune function, and correlate this synergy with clinical response status (MRD, ORR, PFS or OS), blood will be collected serially across the study (see Section 7) for immune phenotyping by flow cytometry and multiplex protein assay. Further, peripheral blood mononuclear cells (PBMCs) will be isolated to assess T cell clonal expansion by next generation sequencing.

Furthermore, changes in bone marrow microenvironment and bone marrow plasma cells from bone marrow biopsies/aspirates collected serially across the study (see Section 7) will be investigated at the cellular and molecular level. At each time point, MRD flow assay will be performed to quantify disease burden and/or assess MM-PC phenotype. In addition, CD138+ plasma cells and CD138- bone marrow microenvironment will be isolated for next generation sequencing (or microarray analysis) to assess plasma cell clonal distribution and T cell clonal expansion respectively. See Section 8.8 for additional details.

Immune Response Analyses

Monoclonal antibody therapy such as elotuzumab can be associated with IRRs such as cytokine release syndrome (CRS). CRS clinically manifests when large numbers of lymphocytes (B cells, T cells and or/ natural killer (NK) cells) become activated and release inflammatory cytokines. Patients can experience these reactions during monoclonal antibody infusion (uniphasic reaction) and/or within hours of an infusion (biphasic/delayed reaction). For subjects potentially experiencing grade ≥ 3 IRR (uniphasic or biphasic), we will conduct immune response analyses (with a particular emphasis on NK or T cell activation and polarization). These analyses may provide valuable insights regarding underlying immunological pathway(s) that could be applied to better prevention of management of such event.

2. OBJECTIVES

2.1 Primary Objective

The primary objective is to evaluate the efficacy of elotuzumab when combined with KRd in terms of very good partial response or better (VGPR+) after induction in subjects with relapsed or refractory multiple myeloma, and compare to relevant historical controls. Response will be assessed based on the International Myeloma Working Group (IMWG) 2016 criteria [22].

2.2 Secondary Objectives

Secondary objectives include evaluation of elotuzumab in combination with KRd by estimating the following:

- Overall response rate (ORR) defined as the percent of subjects achieving a partial response or better per IMWG 2016 criteria [22].

- Progression-free survival (PFS) defined as the time from treatment start (Cycle 1, Day 1) until disease progression or death.
- Overall survival (OS) defined as the time from treatment start until death.
- Time to disease progression (TTP) defined as the time from treatment start until disease progression.
- Duration of response (DoR) in subjects achieving a partial response or better defined as the time from achieving a partial response until disease progression or death.
- Time to next treatment (TTNT) as defined by the time from treatment start until the start of the first subsequent anti-cancer therapy after all protocol directed therapy is completed.

2.3 Safety Objectives

The safety objectives will include evaluation of study drug administration, adverse events assessed by NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03, serious adverse events including deaths on study treatment.

2.4 Exploratory Objectives

- Explore PET/CT response as an imaging correlate end-point.
- Explore minimal residual disease (MRD) by:
 - Flow cytometry
 - NGS
- Characterize KRd-Elotuzumab synergistic activity on NK and T cell function and polarization
- Explore correlation of systemic immune profiling with measurements of clinical response such as MRD, ORR, PFS and OS by performing:
 - Cytokine profiling by multiplex protein assay
 - Blood immunotyping [including NK, NK-T and T cell subsets distribution and activation analyses] by flow cytometry
 - Bone marrow immunotyping by flow cytometry
- Explore correlation of circulating T cell receptor (TCR) repertoire immuno-sequencing by NGS with parameters of clinical response such as MRD, ORR, PFS and OS.
- Explore correlation of peripheral and medullar T cell clonal expansion with MM-PC clonal distribution
- Examine changes in biology of BM and BM plasma cells before and after treatment(s) by B cell receptor (BCR) sequencing and global gene expression profiling
- Explore immune response (with a particular emphasis on NK or T cell activation and polarization) in subjects who experience a grade ≥ 3 IRR

3. SUBJECT SELECTION

3.1 Subject Recruitment

Subjects will be recruited at Levine Cancer Institute (LCI) locations and potentially at other participating sites.

Because no dosing or adverse event data are currently available on the use of elotuzumab in combination with KRd in subjects <18 years of age, children are excluded from this study. In addition, MM is not a disease typically diagnosed in those <18 years of age.

3.2 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Written informed consent and HIPAA authorization for release of personal health information signed by the subject or his/her legally authorized representative.
2. Age \geq 18 years at the time of consent.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2 (see Appendix A, Section 18.1).
4. Documented history of relapsed and/or refractory multiple myeloma per IMWG 2016 criteria [22] as defined below (biochemical and/or clinical relapse per IMWG criteria); (**NOTE:** subjects refractory to bortezomib and/or lenalidomide are eligible; subjects who previously received carfilzomib are eligible provided they experienced a minimal response or better and relapsed >60 days after completion of treatment [see exclusion criteria #2]):
 - a. Relapse is defined as progression of disease after an initial response to previous treatment, more than 6 months after discontinuation of treatment.
 - b. Refractory is defined as lack of response to previous treatment, progression of disease during treatment, or progression of disease within 6 months of discontinuation of treatment.
5. Prior treatment with one line (and no more than one line) of systemic therapy for MM; **NOTE:** A new line of therapy is considered to start when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of progressive disease (PD), relapse, or toxicity or when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease. Induction therapy and stem cell transplant followed by planned maintenance therapy (provided there is no intervening PD) are considered to be a single line.
6. Subject must have recovered from any treatment-induced toxicities to \leq grade 1 or baseline:
7. Adequate washout from previous therapy:
 - a. Prior chemotherapy is completed >3 weeks prior to day 1 of treatment (6 weeks for melphalan, nitrosoureas or monoclonal antibodies).
 - b. Autologous transplant completed (referring to day of stem cell infusion) >12 weeks prior to day 1 of treatment; allogeneic transplant >16 weeks prior to day 1 of treatment.
 - c. Prior radiotherapy completed at least 2 weeks prior to day 1 of treatment.

- d. Corticosteroid therapy at a dose equivalent to dexamethasone >4mg/day has been completed at least 2 weeks prior to day 1 of treatment.
8. Measurable disease defined as:
- Serum M-protein ≥ 0.5 g/dL **OR**
 - Urine M-protein ≥ 200 mg/24 h **OR**
 - Involved free light chain (FLC) level ≥ 10 mg/dL provided serum FLC ratio is abnormal.
9. Demonstrate adequate organ function within 1 week of day 1 of treatment as defined in the table below:

System	Laboratory Value
Hematological	
White Blood Cell (WBC)	$\geq 2,000/\text{mm}^3$
Absolute Neutrophil Count (ANC)	$\geq 1,000/\text{mm}^3$ without growth factors within 1 week of day 1 of treatment
Hemoglobin (Hgb)	≥ 8 g/dL
Platelet count	$\geq 70,000/\text{mm}^3$ if bone marrow plasmacytosis of <50%; otherwise $\geq 50,000/\text{mm}^3$
Renal	
Serum creatinine OR Creatinine clearance	$\leq 1.5 \times$ upper limit of normal (ULN) OR ≥ 40 mL/min as measured by a 24-hour urine collection or estimated by the Cockcroft and Gault formula ¹
Hepatic	
Bilirubin	$\leq 2 \times$ ULN; < 3.0 for subjects with Gilbert's Syndrome
Aspartate aminotransferase (AST)	$\leq 2.5 \times$ ULN
Alanine aminotransferase (ALT)	$\leq 2.5 \times$ ULN
¹ See formula in Appendix B, Section 18.2	

10. Adequate cardiac function as defined by $\geq 45\%$ Left Ventricular Ejection Fraction (LVEF) by ECHO or MUGA within 28 days prior to day 1 of treatment.
11. Females of childbearing potential (FCBP) must have a negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to day 1 of treatment, and be willing to undergo serial serum or urine pregnancy testing. **NOTE:** Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or are postmenopausal (at least 12 consecutive months with no menses without an alternative medical cause).
12. FCBP must be willing to use a highly effective contraceptive method (i.e., achieves a failure rate of <1% per year when used consistently and correctly) plus a second

contraceptive method (considered acceptable [failure rate of >1% per year] or highly effective) from the time of informed consent until 6 months after the last protocol prescribed therapy has been discontinued. **NOTE: estrogens may further increase the risk of thrombosis (beyond that associated with lenalidomide) and their use should be based on a benefit-risk decision.** For the highly effective contraceptive method, a method with low user dependency is preferable but not required (see tables, adapted from: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf).

Highly Effective Birth Control Methods
<ul style="list-style-type: none"> combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation <ul style="list-style-type: none"> oral intravaginal transdermal progestogen-only hormonal contraception associated with inhibition of ovulation <ul style="list-style-type: none"> oral injectable implantable¹ intrauterine device (IUD)¹ intrauterine hormone-releasing system (IUS)¹ vasectomised partner^{1,2} sexual abstinence³
¹ Contraception methods considered to have low user dependency
² Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the FCBP trial participant
³ Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments

Acceptable Birth Control Methods
<ul style="list-style-type: none"> Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action Male or female condom with or without spermicide¹ Cap, diaphragm or sponge with spermicide¹
¹ A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

13. Male subjects (even those who have had a vasectomy) who are sexually active with a FCBP must be willing to use latex or synthetic condoms from the time of informed consent until 180 days after the last protocol prescribed therapy has been discontinued. The FCBP partner should also consider contraception recommendations (see inclusion #11).
14. As determined by the enrolling physician, ability of the subject to understand and comply with study procedures for the entire length of the study.

3.3 Exclusion Criteria

Subjects meeting any of the criteria below may not participate in the study:

1. Discontinuation of previous lenalidomide, carfilzomib or dexamethasone due to intolerance.
2. If previously treated with carfilzomib, lack of response, progression during or relapsed within 60 days after completion of treatment.
3. Any infection, at the time of screening, requiring systemic therapy (i.e. involving IV antibiotics) (**NOTE:** at discretion of investigator, subjects with uncomplicated urinary tract infections may be eligible).
4. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study, and any female subject must agree not to donate eggs during the study and for 4 months after the last protocol prescribed therapy has been discontinued).
5. Has a known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, carcinoma of the prostate with a current PSA value of <0.5 ng/mL or other cancer for which the subject has completed treatment, been disease-free for at least five years, and is considered by Sponsor-Investigator to be at $<30\%$ risk of relapse, or on hormonal therapy for a history of either prostate cancer or breast cancer, provided that there has been no evidence of disease progression during the previous three years.
6. Non-secretory MM.
7. Active involvement of the central nervous system by MM.
8. Prior cardiovascular cerebrovascular accident with persistent neurological deficit.
9. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).
10. Had major surgery within 4 weeks prior to day 1 of treatment.
11. Plasmapheresis within 4 weeks from day 1 of treatment.
12. Treatment with any investigational drug within 4 weeks prior to day 1 of treatment.
13. Uncontrolled clinically significant illness including, but not limited to, uncontrolled hypertension (as per the most updated Joint National Committee for the Management of Hypertension definitions), symptomatic congestive heart failure (as per New York Heart Association [NYHA] class III or IV [see Appendix C, Section 18.3], uncontrolled angina

pectoris, myocardial infarction within the past 6 months, known or suspected amyloidosis, uncontrolled cardiac arrhythmia, psychiatric illness/social situations that would limit compliance with study requirements as determined by the investigator, or any other condition (including laboratory abnormalities) that would, in the opinion of the Sponsor-Investigator, place the subject at unacceptable risk if he/she were to participate in the study.

14. Known allergies, hypersensitivity, or intolerance to monoclonal antibodies or human proteins, elotuzumab or its excipients or known sensitivity to mammalian-derived products, carfilzomib or its excipients, lenalidomide or its excipients, or dexamethasone or its excipients.
15. Known human immunodeficiency virus (HIV) infection or active hepatitis A, B and/or C infection.
 - a. Subjects with resolved HBV infection (i.e. subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Subjects who are PCR positive will be excluded. Exception: subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

3.4 Screen Failures

A subject who, for any reason (e.g., failure to satisfy the selection criteria or withdraws consent), terminates his/her study participation before receiving the first dose of study therapy is regarded as a “screen failure.” All screen failures will be tracked. Enrollment will continue until the targeted sample size in the evaluable population (Section 14.4) is achieved.

4. REGISTRATION

Following informed consent, subjects will be registered by the Coordinating Site and assigned a Study ID number. A subject is considered registered when they are assigned a Study ID number.

5. STUDY PLAN

See Schema (page III).

This single arm, open-label phase II study is designed with the primary objective of evaluating the efficacy of induction therapy comprised of 4 cycles of carfilzomib, lenalidomide, dexamethasone and elotuzumab (KRd+elotuzumab) in terms of VGPR+ in subjects with relapsed or refractory multiple myeloma, and comparing to relevant historical controls. Post induction, all subjects will undergo disease evaluation for assessment of the primary endpoint. Maintenance therapy comprised of elotuzumab and lenalidomide (R+elotuzumab) will start directly after induction and continue until relapse or progression.

This study will initially open as a single center study at LCI and additional investigational site(s) may be added following activation at the coordinating center. We anticipate subjects will be accrued over 24 months.

5.1 KRd+Elotuzumab Induction Regimen

All subjects enrolled will receive KRd+elotuzumab induction. See Section 6 for details on drug administration and dose modifications/delays. **NOTE:** Pre-hydration is required for carfilzomib as described in Section 6.3.2 and premedication is required prior to elotuzumab as described in Section 6.4.1.

Table 1: KRd+Elotuzumab Induction Regimen

Drug	Dose	Route	Schedule	4-Week (28D) Cycle
Carfilzomib ^{a,b}	20 mg/m ²	IV	D1	Cycle 1
Carfilzomib ^{a,b,c}	56 mg/m ²	IV	D8, 15	Cycle 1
Carfilzomib ^{a,b,c}	56 mg/m ²	IV	D1, 8, 15	Cycles 2-4
Lenalidomide	25 mg ^d	Oral	Once a day at bedtime on D1-21	Cycles 1-4
Dexamethasone ^g	28 mg	Oral	Once weekly ^e on D1, 8, 15, 22	Cycles 1-2
	8 mg	IV		
Dexamethasone ^{e,g}	28 mg	Oral	D1	Cycles 3-4
	8 mg	IV		
Dexamethasone ^{f,g}	40 mg	PO	Once weekly on D8, 15 and 22	Cycles 3-4
Elotuzumab ^b	10 mg/kg	IV	Once weekly on D1, 8, 15, 22	Cycles 1-2
Elotuzumab ^b	20 mg/kg	IV	D1	Cycles 3-4

^a Calculate the dose using the subject's actual body surface area (BSA) at baseline. For subjects with a BSA >2.2m², calculate the dose based upon a BSA of 2.2m².

^b If a subject's weight changes by more than 10% from induction cycle 1 day 1 the dose of carfilzomib and elotuzumab should be recalculated. This re-calculated weight should be used as the new baseline weight. **NOTE:** use the subject's actual (not ideal) body weight for dosing as per the American Society of Clinical Oncology (ASCO) guidelines in dosing of obese adult subjects.

^c **NOTE:** In subjects who enroll with a bilirubin and/or AST >1 x ULN, the starting dose of carfilzomib of 20mg/m² should be maintained and not increased to 56mg/m². The dose may be escalated to 56 mg/m² if both bilirubin and AST resolve to ≤ ULN.

^d For subjects who enroll with a CrCl between 40-50 mL/min, the starting dose of lenalidomide may be reduced to 10mg at the discretion of the investigator.

^e On days when elotuzumab is administered: 28mg PO between 3-24 hours prior to start of elotuzumab **OR** as a split dose of 12 mg 12-24 hours and 16 mg 3 hours prior to elotuzumab; 8 mg IV 45 to 90 minutes prior to elotuzumab infusion. **NOTE:** This will serve as the corticosteroid premedication for elotuzumab on days when elotuzumab is administered during induction

^f May administer 20 mg dexamethasone for subjects ≥ 75 years old

^g Oral dexamethasone may be reduced per investigator discretion. On days when elotuzumab is administered, this is allowable after C1 of induction has completed without an infusion-related reaction.

5.2 R+Elotuzumab Maintenance Regimen

The first cycle of maintenance therapy will begin 4 weeks (28D) after the start of cycle 4 of induction. **NOTE:** premedication (including dexamethasone) is required prior to elotuzumab as described in Section 6.4.1.

Table 2: R+Elotuzumab Maintenance Regimen

Drug	Dose	Route	Schedule	4-Week (28D) Cycle
Lenalidomide	15 mg or LTD if <15mg ^a	Oral	Once a day at bedtime on D1-21	Cycles 1-n
Elotuzumab	20 mg/kg ^b	IV	D1 of each cycle	Cycles 1-n
^a LTD=last tolerated dose ^b If a subject's weight changes by more than 10% from cycle 1 day 1 of induction the dose of elotuzumab should be recalculated. This re-calculated weight should be used as the new baseline weight.				

6. TREATMENT DETAILS AND DOSE MODIFICATIONS/DELAYS

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Study Calendar. Toxicity will be assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), v4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Note: In each dose modification table in Section 6, the Recommended Action is per investigator's discretion.

6.1 General Rules for Dose Modifications/Delays for KRd+Elotuzumab Induction

In the event of a possible drug-related toxicity, the investigator should, to the best of his/her ability, assess its relationship to each of the drugs within the regimen (carfilzomib, lenalidomide, dexamethasone, elotuzumab), or to the combination to the extent possible. Actions outlined in the sections below should be instituted for the agent(s) considered likely to be involved.

If the dose of one drug in the KRd+elotuzumab regimen is delayed, interrupted, or discontinued, the treatment with the other drugs may continue as scheduled. However, if elotuzumab is permanently discontinued, the subject should be removed from protocol-mandated treatment, and followed up per protocol (KRd may continue off protocol at the discretion of the investigator). If dexamethasone is delayed or discontinued during induction, the administration of elotuzumab should be at the discretion of the investigator and based on clinical judgment (i.e., risk of hypersensitivity).

Subjects experiencing a 28-day delay in elotuzumab due to an elotuzumab-related AE must be discontinued from protocol-mandated treatment and followed up per protocol.

While dose delays or interruptions are permitted, the start of each cycle cannot be delayed and is fixed relative to Cycle 1 Day 1 of induction. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Missed doses should be skipped, not delayed, as detailed in the rules in the sections below.

6.2 General Rules for Dose Modifications/Delays for R+Elotuzumab Maintenance

In the event of a possible drug-related toxicity, the investigator should, to the best of his/her ability, assess its relationship to elotuzumab, lenalidomide, or to the combination to the extent possible. Actions outlined in the sections below should be instituted for the agent(s) considered likely to be involved.

If the dose of elotuzumab is delayed or interrupted, treatment with lenalidomide may continue as scheduled. However, if elotuzumab is permanently discontinued, the subject should be removed from protocol-mandated treatment, and followed-up per protocol (lenalidomide may continue off protocol at the discretion of the investigator). If lenalidomide is held or discontinued, treatment with elotuzumab may continue as scheduled.

Subjects experiencing a 28-day delay in elotuzumab due to an elotuzumab-related AE must be discontinued from protocol-mandated treatment and followed up per protocol.

While dose delays or interruptions are permitted, the start of each cycle cannot be delayed and is fixed relative to Cycle 1 Day 1 of maintenance. Adjustments to the Cycle 1 Day 1 anchored schedule should not be performed. Missed doses should be skipped, not delayed, as detailed in the rules in the sections below.

6.3 Carfilzomib

6.3.1 Administration

Subjects with active or suspected infection of any kind that require systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with an anti-infective(s), the course of antibiotics has been completed.

Subjects will receive carfilzomib as an intravenous (IV) infusion over approximately 30 minutes as per the dose and schedule outlined in Table 1 for induction. If the subject has a dedicated line for carfilzomib administration, the line must be flushed with a minimum of 20 mL of normal saline prior to and after drug administration. The dose must be administered at a facility capable of managing IRRs.

On the days both carfilzomib and elotuzumab are due to be administered, carfilzomib will be administered first.

6.3.2 Pre- and Post-Dose Hydration and Monitoring Cycles 1 and 2 of Induction

Starting at least 48 hours before Cycle 1 Day 1 of induction, subjects should be instructed to ingest oral hydration as follows: 30 mL/kg/day (approximately 6 to 8 cups of liquid per day) continuing up to the time of treatment. Subject compliance must be assessed before initiating treatment, which is to be delayed if oral hydration is not adequate. In subjects considered at risk for tumor lysis syndrome (TLS; i.e., those with high tumor burden), oral hydration should be continued in Cycle 2 and beyond as required by the

subject's medical condition and at the investigator's discretion. See Section 6.8.1 for recommended concomitant medications.

IV hydration will be given immediately prior to the first two doses of carfilzomib during Cycle 1 of induction. This will consist of 250 to 500 mL normal saline or other appropriate IV fluid. Subjects will remain at the clinic under observation for at least 1 hour following the first 2 doses of carfilzomib in Cycle 1 of induction. During these observation times, post dose IV hydration (between 250 mL and 500 mL normal saline or other appropriate IV fluid formulation) will be given. Subjects should be monitored periodically during this period for evidence of fluid overload. After the second dose of Cycle 1, pre- and/or post-hydration may be administered at the discretion of the investigator. If, however, lactate dehydrogenase (LDH) or uric acid is elevated (and/or in subjects considered still at risk for TLS) after the second dose in Cycle 1 of induction, then the recommended IV hydration should be given additionally before each remaining dose in Cycle 1. The goal of the hydration program is to maintain robust urine output (e.g. ≥ 2 L/day). Subjects should be monitored periodically during this period for evidence of fluid overload.

6.3.3 First Dose Effect for Carfilzomib during Induction

A "first dose effect" has been seen with carfilzomib, which is notable for fever, chills, rigors, and/or dyspnea occurring during the evening following the first day of infusion and an increase in creatinine on Day 2, which may be the clinical sequelae of rapid tumor lysis and/or cytokine release. Should a "first dose" effect occur at any point during Cycle 1 or 2 of induction, treatment with high dose glucocorticoids (e.g. methylprednisolone 50–100 mg) is recommended. In addition, intravenous fluids, vasopressors, oxygen, bronchodilators, and acetaminophen should be available and instituted, as medically indicated.

6.3.4 Dose Modifications for Carfilzomib-Related Toxicities

If a dose of carfilzomib is missed because of toxicities, the subject should not be administered an additional dose, but should be given the next usual prescribed dose.

Refer to the following table for carfilzomib dose levels when dose reductions are required during induction:

Table 3: Dose Levels for Carfilzomib during Induction

Dose Level	Dose
0*	56 mg/m ²
-1	45 mg/m ²
-2	36 mg/m ²
-3	27 mg/m ²

*Dose level 0 is the starting dose.

If dose reductions of carfilzomib beyond those levels listed in Table 3 are required, this agent should be permanently discontinued.

6.3.4.1 Hematologic Toxicities

NOTE: Thrombocytopenia has been transient and typically resolves during the week between treatments.

Table 4: Dose Modifications for Hematologic Toxicities

Toxicity	Recommended Action
ANC < 500/mm ³	<ul style="list-style-type: none"> First occurrence: Hold dose; resume at same dose level once ANC recovers to $\geq 500/\text{mm}^3$ For any recurrence: hold dose; resume with dose reduced by 1 level once ANC recovers to $\geq 500/\text{mm}^3$
ANC < 500/mm ³ and temperature >38.5°C or 2 consecutive readings of >38.0°C for 2 hours	<ul style="list-style-type: none"> Hold dose; resume at same dose level once ANC returns to baseline and fever resolves
Platelets < 10,000/mm ³ or evidence of bleeding with thrombocytopenia	<ul style="list-style-type: none"> First occurrence: Hold dose; resume at same dose level once platelets recover to $\geq 10,000/\text{mm}^3$ and/or bleeding is controlled For any recurrence, hold dose; resume with dose reduced by 1 level once platelets recover to $\geq 10,000/\text{mm}^3$ and/or bleeding is controlled

6.3.4.2 Non-Hematologic Toxicities

Creatinine clearance (CrCl) changes associated with carfilzomib are mostly transient, reversible, and non-cumulative. Renal function must be monitored closely during treatment with carfilzomib. Serum chemistry values, including creatinine, must be obtained and reviewed prior to each dose of carfilzomib on Day 1, 8, and 15 during induction. Creatinine clearance should be calculated on Day 1 of each cycle.

Carfilzomib treatment can cause nausea, vomiting, diarrhea, or constipation sometimes requiring the use of antiemetics or antidiarrheals. Fluid and electrolyte replacement should be administered as clinically indicated to prevent dehydration.

Subjects with active or suspected infection of any kind that require systemic treatment should not be dosed with carfilzomib until the infection has resolved and if being treated with an anti-infective(s), the course of antibiotics has been completed.

Subjects with a history of HBV should be closely monitored for signs and symptoms of active HBV infection throughout treatment with carfilzomib, including the 30-day safety monitoring follow-up period.

Subjects receiving carfilzomib should be monitored for any new or worsening neurologic, cognitive or behavioral signs and symptoms that may be suggestive of Progressive Multifocal Leukoencephalopathy (PML) as part of the differential diagnosis of central nervous system disorders. If PML is suspected, subjects should be referred to a specialist and appropriate diagnostic testing should be initiated. If a PML diagnosis is confirmed, carfilzomib should be permanently discontinued.

Table 5: Dose Modifications for Non-hematologic Toxicities

Toxicity	Recommended Action
Serum creatinine ≥ 2 X baseline or CrCl < 15 mL/min, or CrCl decreases to $\leq 50\%$ of baseline, or need for hemodialysis (Creatinine clearance only applicable for Day 1 of each cycle)	<ul style="list-style-type: none"> • Hold dose and continue monitoring renal function • If attributable to carfilzomib, resume with dose reduced by 1 level once renal function has recovered to within 25% of baseline • If not attributable to carfilzomib, dosing may be resumed at discretion of investigator • If on hemodialysis, administer the dose after the hemodialysis procedure
In subjects who enroll with bilirubin and AST $< \text{ULN}$ at baseline, and bilirubin increases to >1 to $3 \times \text{ULN}$ and/or AST increases to $> \text{ULN}$	<ul style="list-style-type: none"> • Hold dose; resume with dose reduced by 1 level once resolved or returned to baseline
In subjects who enroll with bilirubin and/or AST $> \text{ULN}$ at baseline, and bilirubin and/or AST increases by 1 grade	<ul style="list-style-type: none"> • Hold dose; resume with dose reduced by 1 level once resolved or returned to baseline
\geq Grade 3 non-hematologic toxicity ^a	<ul style="list-style-type: none"> • Hold dose; resume with dose reduced by 1 level once resolved or returned to baseline
If Posterior Reversible Encephalopathy Syndrome (PRES) is suspected	<ul style="list-style-type: none"> • Hold dose; consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. • If confirmed, permanently discontinue carfilzomib • If the diagnosis of PRES is excluded and if clinically appropriate, restart dose administration • If PRES recurs, permanently discontinue carfilzomib
If thrombotic microangiopathy (TMA) (TTP/HUS) is suspected	<ul style="list-style-type: none"> • Hold dose; and manage per standard of care including plasma exchange as clinically appropriate • If TMA is confirmed and related to carfilzomib, permanently discontinue • If diagnosis is excluded, carfilzomib can be re started at the previous dose • If the condition recurs, permanently discontinue carfilzomib

Hypertensive Urgency/emergency (defined as sustained or persistent SBO \geq 180 mmHg or DBP \geq 110mmHg)	<ul style="list-style-type: none"> Hold dose until resolution to baseline and restart at 1 dose decrement
If Progressive Multifocal Leukoencephalopathy (PML) is suspected	<ul style="list-style-type: none"> Withhold carfilzomib; refer promptly to a specialist; appropriate diagnostic testing should be initiated If a diagnosis of PML is confirmed, permanently discontinue carfilzomib
Active HBV reactivation	<ul style="list-style-type: none"> Withhold carfilzomib until the infection is adequately controlled. If the benefits outweigh the risks, carfilzomib may be resumed with concomitant prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.
Active or suspected infection of any kind that requires systemic treatment	<ul style="list-style-type: none"> Hold carfilzomib until the infection has resolved and the course of antibiotics has been completed, if being treated with an anti-infective(s)
^a Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or Grade 3 fatigue or asthenia that lasts <7 days	

6.4 Elotuzumab

6.4.1 Premedication

6.4.1.1 In Subjects Without a Prior Infusion-Related Reaction (IRR):

- Dexamethasone (if not already scheduled as part of induction):
 - 28 mg PO (between 3 - 24 hours prior to the start of elotuzumab infusion **OR** as a split dose of 12 mg 12 – 24 hours and 16mg 3 hours prior to elotuzumab) **AND**
 - 8 mg IV (45-90 minutes prior to the start of infusion)
- Note:** Every attempt should be made to administer 8 mg IV dose of dexamethasone prior to each elotuzumab dose; oral dexamethasone may be reduced per investigator discretion. On days when elotuzumab is administered, this is allowable after C1 of induction has completed without an infusion-related reaction. H1 blocker: diphenhydramine (25 - 50 mg PO or IV) or equivalent 45-90 minutes prior to the start of infusion. Note: The diphenhydramine dose can be decreased or discontinued per investigator discretion after at least (3) doses of elotuzumab have been infused without infusion-related reaction.
- H2 blocker: ranitidine 50 mg IV or equivalent 45-90 mins prior to the start of infusion
- Acetaminophen: 650 - 1000 mg PO 45-90 mins prior to the start of infusion

6.4.1.2 In Subjects with a Prior Infusion-Related Reaction (IRR):

- Dexamethasone: see Table 6 below
- H1 blocker: diphenhydramine 50 mg PO or IV or equivalent 45-90 minutes prior to the start of infusion)
- H2 blocker: ranitidine 50 mg IV or equivalent 45-90 mins prior to the start of infusion
- Acetaminophen: 1000 mg PO 45-90 mins prior to the start of infusion

Table 6: Dexamethasone Premedication for Subjects with a Prior IRR

Prior IRR Grade	Dexamethasone Dose and Schedule
≤ 1	28 mg PO (between 3 - 24 hours prior to the start of elotuzumab infusion OR as a split dose of 12 mg 12 – 24 hours and 16 mg 3 hours prior to elotuzumab) AND 8 mg IV (45-90 minutes prior to the start of infusion)
2	28 mg PO (between 3 - 24 hours prior to the start of elotuzumab infusion OR as a split dose of 12 mg 12 – 24 hours and 16 mg 3 hours prior to elotuzumab) AND 10 mg IV^a (45-90 minutes prior to the start of infusion)
3 or recurrent Grade 2	8 mg 12 – 24 hours and 8 mg 3 hours prior to elotuzumab AND 18 mg IV^a (45-90 minutes prior to the start of infusion)
4	Elotuzumab should not be given, see Section 6.4.2
^a If dose modification of dexamethasone is required in a subject with a prior grade 2 or 3 IRR, the dose of dexamethasone to be administered on the day of elotuzumab administration (45 to 90 minutes prior) should not be < 8mg IV.	

6.4.2 Administration

See Section 10.1.2 for preparation of elotuzumab for administration.

See Section 6.4.4 for management of any IRR. See below for elotuzumab infusion rates:

Table 7 Infusion Rate for Elotuzumab 10 mg/kg

Cycle 1 Day 1 (first dose)		Cycle 1 Day 8 (second dose)		Cycle 1 Days 15&22 and all subsequent doses
Time Interval	Rate	Time Interval	Rate	Rate
0-30 min	0.5mL/min	0-30 min	3 mL/min	5 mL/min
30-60 min	1 mL/min	30 min or more	4 mL/min	
60 min or more	2 mL/min	-	-	

The first dose of elotuzumab will be administered following premedication to each subject as an IV infusion, using an automated infusion pump set at an initial rate of 0.5mL per minute (30 mL/hour). The infusion is to be administered through a sterile, non-pyrogenic, low protein binding in line filter (with a pore size of 0.2-µm to 1.2-µm). If the subject does not have an IRR within 30 minutes, escalate the infusion rate by 0.5 mL per minute. If the subject still does not have an IRR within 30 minutes, escalate the infusion rate to a maximum of 2 mL per minute (120 mL/hour).

The second dose of elotuzumab should be initiated at an infusion rate of 3 mL per minute if no IRR were reported with the first elotuzumab infusion. If the subject does not

experience an IRR during the first 30 minutes of the second dose of elotuzumab, escalate the infusion rate by 1 mL per minute to a maximum infusion rate of 4 mL per minute.

The third and fourth dose of elotuzumab should be initiated at an infusion rate of 5 mL per minute if no IRR were reported with previous elotuzumab infusions.

Elotuzumab administered at the 20 mg/kg dose should be infused as indicated below. Subjects who have escalated to 5mL/min at the 10 mg/kg dose must decrease the rate to 3 mL/min at the first infusion at 20 mg/kg. The infusion rate may be increased in a stepwise fashion as described in Table 8 if no infusion reactions develop.

Table 8 Infusion Rate for Elotuzumab 20 mg/kg

Dose 1 (at 20 mg/kg)		Dose 2 and all subsequent doses
Time Interval	Rate	Rate
0-30 min	3 mL/min	5 mL/min
30 min or more	4 mL/min	

6.4.3 Dose Delays for Elotuzumab

No dose reductions of elotuzumab are allowed.

Table 9: Allowed Delays of Elotuzumab Based on Schedule

	Frequency	If Dose Delay:	Dosing Resumption
Induction	Weekly	>2 days, miss dose	next planned weekly dosing date
Induction and Maintenance	Every 4 weeks	>14 days, miss dose	next planned dosing date

6.4.3.1 Infusion-Related Reaction (IRR)

Table 10: Management of Elotuzumab IRR

Grade	Management
1	No intervention required, however, increased monitoring is recommended.
2 or 3 ^a during infusion	Interrupt infusion. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

	<p>Once the IRR has resolved to grade ≤ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the IRR occurred. If no recurrence of the IRR, the escalation regimen can be resumed. Subjects who experience an IRR require vital signs to be monitored every 30 minutes for 1 or 2 hours after the end of the elotuzumab infusion (as clinically indicated). If the elotuzumab IRR recurs, the infusion must be stopped and not restarted on that day. Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion with additional premedication.</p> <p>Subjects should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the IRR occurred. If no grade ≥ 2 IRR recurs, the escalation regimen may be resumed, and the next infusion may be initiated as planned per regimen.</p>
2 or 3^a after completion of infusion	<p>Treat the subject as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.</p> <p>Subjects should have the next infusion started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes) to the rate at which the IRR occurred. If no grade ≥ 2 IRR recurs, the escalation regimen may be resumed, and the next infusion may be initiated as planned per regimen.</p>
4^a	Permanently discontinue elotuzumab infusion.
^a In the event of a grade ≥ 3 IRR, every attempt will be made to draw 15mL of blood, as soon as reasonably possible after the reaction if the subject is still in the infusion clinic. See Section 8.8.2 for additional information.	

6.4.3.2 Other Elotuzumab-Related Toxicities (Non-IRR)

Delay elotuzumab for any \geq grade 3 toxicity (non-IRR) considered at least possibly related to elotuzumab. Treatment may resume once levels resume to baseline or \leq grade 1.

6.5 Lenalidomide

6.5.1 Administration

Lenalidomide is self-administered and should be taken orally at about the same time each day (at bedtime) with water. It may be taken on a full or empty stomach. Subjects should not break, chew or open capsules. Missed doses of lenalidomide will not be made up. If a dose of lenalidomide is missed and it has been <12 hours since the subject's regular dosing time, the subject should take the dose. If it has been ≥ 12 hours, the subject should skip that dose. The subject should not double up on the next dose.

6.5.2 Dose Modification for Lenalidomide-Related Toxicities

Refer to the following table for lenalidomide dose levels when dose reductions are required during induction or maintenance:

Table 11: Dose Levels for Lenalidomide*

Dose Level	Dose	Schedule
0**	25 mg	D1-21
-1	15mg	D1-21
-2	10mg	D1-21
-3	5mg	D1-21
-4	2.5mg	D1-21
-5	2.5mg	Every other day during D1-21

*If dose reduction required due to renal dysfunction, see Section 6.5.2.2 Table 11.

**Dose level 0 is the starting dose.

6.5.2.1 Hematologic Toxicities

Table 12: Dose Modifications for Hematologic Toxicities

Toxicity	Recommended Action
ANC < 1000/mm ³	<ul style="list-style-type: none"> Interrupt lenalidomide Resume at same dose level once ANC recovers to $\geq 1000/\text{mm}^3$ For any recurrence, interrupt lenalidomide; resume with dose reduced by 1 level once ANC recovers to $\geq 1000/\text{mm}^3$
Platelets < 30,000/mm ³ or evidence of bleeding with thrombocytopenia	<ul style="list-style-type: none"> Interrupt lenalidomide Resume with dose reduced by 1 level once platelet count recovers to $\geq 30,000/\text{mm}^3$ For any recurrence, interrupt lenalidomide; resume with dose reduced by 1 level once platelets recover to $\geq 30,000/\text{mm}^3$

6.5.2.2 Dosing in Renal Impairment

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the dose of lenalidomide are recommended in subjects with renal impairment. The recommended doses for subjects with multiple myeloma and renal impairment are shown in the table below.

Table 13: Dose Modifications for Renal Impairment

Dose modifications related to creatinine clearance only apply to Day 1 of each cycle.

Toxicity	Recommended Action
CrCl 30 to 50 mL/min	<ul style="list-style-type: none"> Ensure daily dose is no higher than 10mg every 24 hours
CrCl <30mL/min and not requiring dialysis	<ul style="list-style-type: none"> Ensure dose is no higher than 15 mg, and reduce frequency to every 48 hours
CrCl <30mL/min requiring dialysis	<ul style="list-style-type: none"> Ensure daily dose is no higher than 5 mg every 24 hours; on dialysis days, administer the dose following dialysis.

6.5.2.3 Other Non-Specified Non-Hematologic Toxicities

Table 14: Dose Modifications for Non-Hematologic Toxicities

Toxicity	Recommended Action
Other ≥ grade 3 non-hematologic toxicity ^a	<ul style="list-style-type: none"> Hold dose; resume with dose reduced by 1 level once resolved to ≤ grade 2
^a Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or grade 3 fatigue or asthenia that lasts <7 days	

6.6 Dexamethasone

6.6.1 Administration

For induction, the dexamethasone total oral dose of 28 mg may be given 3-24 hours prior to start of elotuzumab **OR** as a split dose of 12 mg 12-24 hours and 16 mg 3 hours prior to elotuzumab at the discretion of the investigator. Forty-five to 90 minutes prior to elotuzumab infusion, administer 8 mg dexamethasone IV. Oral dexamethasone may be reduced per investigator discretion. On days when elotuzumab is administered, this is allowable after C1 of induction has completed without an infusion-related reaction. During maintenance when dexamethasone is administered as premedication only, any dose modifications required should be made at the discretion of the investigator. However, when using as a premedication, every attempt should be made to maintain the 8 mg dexamethasone IV.

Refer to the following table for dexamethasone dose levels when dose reductions are required during induction:

Table 15: Dose Levels for Dexamethasone during Induction on Elotuzumab Dosing Days

Dose Level	PO	IV
0	28 mg	8 mg
-1	12 mg	8 mg
-2	0 mg	8 mg

If dose reductions of dexamethasone beyond those levels listed in Table 13, this agent should be permanently discontinued.

Table 16: Dose Levels for Dexamethasone during Induction on NON-Elotuzumab Dosing Days

Dose Level	PO
0	40 mg
-1	20 mg
-2	12 mg

6.6.2 Dose Modifications for Dexamethasone-Related Toxicities

If a dose of dexamethasone is missed, the subject should not take an additional dose, but should take the next usual prescribed dose.

Oral dexamethasone may be reduced per investigator discretion. On days when elotuzumab is administered, this is allowable after C1 of induction has completed without an infusion-related reaction.

Table 17: Dose Modifications for non-Hematologic Toxicities

Toxicity	Recommendation Action
Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
≥Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart dexamethasone reduced by 1 dose level; consider concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist

	despite above measures, discontinue dexamethasone permanently.
Acute pancreatitis	Discontinue dexamethasone permanently.
Edema \geq Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and restart dexamethasone reduced by 1 dose level; if edema persists despite above measures, decrease dose another level. Discontinue dexamethasone permanently if symptoms persist despite second reduction.
Confusion or mood alteration \geq Grade 2 (interfering with function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart dexamethasone reduced by 1 dose level. If symptoms persist despite above measures, reduce by another dose level.
Muscle weakness \geq Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone by 1 dose level. If weakness persists, decrease dose by 1 more dose level. Discontinue dexamethasone permanently if symptoms persist.
Hyperglycemia \geq Grade 3	Treatment with insulin or other hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 1 dose level until levels are satisfactory.
Insomnia \geq Grade 2	Hold dexamethasone until symptoms resolve. Restart dexamethasone reduced by 1 dose level once symptoms resolve.
Other non-hematologic toxicity \geq Grade 3 felt related to dexamethasone ^a	Hold dexamethasone dose. Resume dexamethasone reduced by 1 dose level when toxicity has resolved to \leq Grade 2 or to baseline. If toxicity recurs, discontinue dexamethasone permanently.
^a Other than nausea, vomiting or diarrhea that responds to supportive care within 7 days, or Grade 3 fatigue or asthenia that was present at baseline or that lasts <7 days	

6.7 Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Subjects may receive palliative radiation at the discretion of the Sponsor-Investigator.

6.8 Concomitant Medication

6.8.1 Recommended Medications

6.8.1.1 Bisphosphonates

For subjects who have not previously received bisphosphonates, bisphosphonates are recommended for all subjects. Bisphosphonate therapy is recommended to be continued per treatment guidelines. In addition, denosumab use is also permitted.

6.8.1.2 Allopurinol

It is recommended that subjects at high risk for TLS (i.e., those with a high tumor burden, high LDH and/or high uric acid level before the start of treatment) be treated prophylactically in accordance with local standards including allopurinol 300 mg daily.

6.8.1.3 Anti-Viral

Acyclovir or equivalent antiviral should be given to all subjects to decrease the risk of herpes zoster reactivation, per institutional prophylaxis guidelines, unless contraindicated.

Prophylaxis with antivirals should be considered in subjects who are carriers of HBV.

6.8.1.4 Thromboprophylaxis

Thromboprophylaxis is recommended for all subjects receiving the combination of carfilzomib, lenalidomide and dexamethasone. The regimen of thromboprophylaxis should be based on an assessment of the subject's underlying risks. Instruct subjects to report immediately any signs and symptoms suggestive of thrombotic events.

6.8.2 Prohibited Medications

Concomitant administration of investigational agents, other than those mandated by the protocol, are prohibited.

No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the subject's malignancy.

6.8.3 Permitted Medications

Subjects may receive antiemetics and antidiarrheal agents as necessary. Myeloid growth factors may be used if neutropenia occurs but should not be given prophylactically. Subjects may receive platelet transfusions if clinically indicated in accordance with institutional guidelines. Subjects should have anemia treated in accordance with the institutional guidelines (however, see Section 6.8.3.1).

All other treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

6.8.3.1 Precautionary Medications

If an erythropoietic stimulating agents (ESAs) is given for anemia, keep in mind that there is an increased risk of thrombosis with lenalidomide and carfilzomib. Include all concomitant medications that are not specifically prohibited but require additional monitoring during study treatment.

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7. STUDY CALENDAR

Study Procedures	Screening ¹	Induction Cycles 1-2 ²				Induction Cycles 3-4 ²				Maintenance Cycles 1+ ⁴	Safety Follow-up Visit ⁵	Follow-up ⁶
Study Day		D1 ¹	D8	D15	D22	D1	D8	D15	D22	D1 ³		
Informed Consent	X											
Medical history	X											
Physical exam ^{7,22}	X	X				X				X	X	
ECOG Performance status ²²	X	X				X				X	X	
Vital signs ⁸	X	X	X	X	X	X				X	X	
ECG	X	X				X					X	
ECHO or MUGA	X											
Hepatitis B virus (HBV) serology ²⁰	X	X Subjects with unknown HBV status who are currently receiving treatment with carfilzomib should be tested for HBV infection										
HBV DNA testing ²¹	X	X Only required in subjects receiving carfilzomib not previously tested in screening who have serologic evidence of resolved HBV infection										
Serum chemistries ⁹	X	X	X	X	X	X	X	X		X	X	
CBCD ¹⁰	X	X	X	X	X	X	X	X		X	X	
Pregnancy test ¹¹	X	See footnote #11										
AEs & concomitant meds	X	Monitor continuously (see Section 12.3 for timing of AE/SAE collection)										
Serum beta2-microglobulin	X											
Blood and urine for disease evaluation ¹²	X	X				X				X ³		
Bone marrow aspirate and biopsy ¹³	X									X Post-induction and CR		
Skeletal Survey ¹⁴	X	As clinically indicated										
Assess extramedullary plasmacytomas ¹⁵	X	Assess at CR and/or if clinically indicated										
Carfilzomib ¹⁶		X	X	X		X	X	X				
Lenalidomide		Days 1-21 (oral) each cycle				Days 1-21 (oral) each cycle				Days 1-21 (oral) each cycle		
Dexamethasone ¹⁷		X	X	X	X	X	X	X	X			
Elotuzumab ¹⁸		X	X	X	X	X				X		

Blood sample for correlatives ¹⁹		X				X				X		
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Key to Footnotes

¹ Within 28 days prior to induction cycle 1 day 1 (C1D1) unless otherwise noted; if screening hematology and serum chemistries were performed within 7 days of induction C1D1, these do not need to be repeated C1D1 of induction; if screening ECG was performed within 14 days of induction C1D1, an ECG does not need to be repeated C1D1 of induction.

² A window of +/- 2 days will be applied to all induction treatment study visits (includes treatment and required procedures). Every effort should be made to maintain consecutive dosing days.

³ The post-induction disease evaluation (blood and urine collection and bone marrow biopsy/aspirate) should occur within 7 days prior to treatment on C1D1 of maintenance. The primary endpoint (VGPR or better post induction) will be assessed at this post-induction disease evaluation. See Section 13.1 for details on efficacy evaluations and note that all response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments.

⁴ A window of +/- 14 days will be applied to all maintenance study visits (includes treatment and required procedures).

⁵ This visit should occur in subjects 30 days (+/-10 days) after treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). **NOTE:** subjects who have ongoing Grade 4 AE or SAE at the time of the Safety Follow-up Visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.

⁶ For subjects who discontinue study treatment before relapse or PD, disease evaluations should continue to be performed until relapse or confirmed PD, death, start of a new anticancer treatment, withdrawal of consent to study participation, or end of the study, whichever occurs first. The schedule for disease evaluation should follow the schedule outlined during maintenance. Survival follow-up will occur every 3 months (+/- 30 days) from the last administration of protocol-directed therapy or until death, and may be conducted via telephone. Any second primary malignancies discovered during long-term follow-up will be documented.

⁷ Complete physical exam at screening with evaluation by body system, including height, weight and neurologic exam to detect peripheral neuropathy. Thereafter symptom-directed physical exam (to include weight) only. Subjects should also be monitored for second primary malignancies. If a subject's weight changes by more than 10% from induction C1D1, the dose of carfilzomib and elotuzumab should be re-calculated. This re-calculated weight should be used as the new baseline weight.

⁸ Vital signs (to include temperature, heart rate, blood pressure and respiratory rate) should be recorded at screening, before each elotuzumab infusion, and at the Safety Follow-up Visit.

⁹ Serum chemistries: BUN, creatinine, (with calculated creatinine clearance at screening and on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin. Magnesium testing NOT required on C1D2

¹⁰ CBCD: complete blood count with differential and platelets.

¹¹ If the screening serum B-HCG in FCBP is done within 24 hours prior to induction C1D1, it does not need to be repeated on C1D1. Pregnancy testing (serum or urine) must be repeated once a week (D1, 8, 15, 22) in induction cycle 1, and then monthly (D1 of each cycle) for subsequent cycles in FCBP.

¹² Tests to include: serum quantitative immunoglobulins (QIg; including IgA, IgM, IgG, IgD, IgE), serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP; 24-hr urine sample required), serum and urine immunofixation, and serum free light chain (FLC). If screening tests were performed within 14 days of induction C1D1, these do not need to be repeated C1D1 of induction. Testing for IgD and IgE will only be

performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed on D1 of each cycle for subjects with light chain only disease and for subjects where a CR is suspected or maintained. After screening assessments, subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated. Starting at maintenance cycle 14, disease evaluations should only be collected every 2 cycles (i.e., cycle 14, 16, 18, etc.)

¹³ Bone marrow aspirate and biopsy collected for disease assessment and correlative analyses at screening (pre-induction), post-induction (within 7 days prior to treatment on C1D1 of maintenance) and to confirm a CR. A bone marrow biopsy and aspirate will also be collected at relapse/progression for disease assessment and correlative studies at the discretion of the investigator. During maintenance, bone marrow biopsies and aspirates will be collected every 6 months (+/- 30 days) for disease evaluation per standard of care. See Section 8.8.3 for additional details.

¹⁴ Acceptable for screening if performed as part of standard of care within 42 days prior to induction C1D1.

¹⁵ Assess extramedullary plasmacytomas at screening using PET/CT and/or Whole Body (WB)-MRI for subjects with a history of plasmacytomas or if clinically indicated. Acceptable for screening if performed as part of standard of care within 42 days prior to induction C1D1.

¹⁶ See Section 6.3 for required hydration and additional information regarding cycle 1 dosing.

¹⁷ See Section 5.1 for dosing information. For maintenance, dexamethasone is given as a premedication for elotuzumab, but is not considered part of the regimen.

¹⁸ See Section 6.4.1 for required premedication. Any time a grade 3 or higher IRR is observed during the study, every attempt should be made to draw an unscheduled blood sample (15) as soon as possible after the reaction for potential immune response analysis (see Section 6.4.4, Table 8)

¹⁹ Peripheral blood (total of 15mL) will be collected before treatment on D1 of each induction cycle, before treatment on D1 of maintenance cycle 1, cycle 3 and then every third maintenance cycle thereafter (i.e., cycle 6, 9, etc.), and at progression/relapse. See Section 8.8.1 for detailed information.

²⁰ Local testing for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) for all subjects in screening. Subjects not previously tested for HBV at screening with unknown HBV status currently receiving treatment with carfilzomib should be tested for HBV. For subjects currently receiving treatment with carfilzomib, every effort should be made to perform the HBV testing within 8 weeks of IRB approval Version 4 of protocol.

²¹ For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) at Screening or for subjects with unknown HBV status currently on carfilzomib tested for HBV per Footnote #21. HBV DNA testing by PCR must be performed locally. Subjects with serologic findings suggestive of HBV vaccination (Anti-HBs positivity as the only serologic marker) and a known history of prior HBV vaccination do not need to be tested for HBV DNA by PCR.

²² For office visits required during the COVID-19 pandemic, virtual visits will be allowed per investigator discretion starting with Cycle 2 Day 1 induction. This includes physical exam and performance status.

8. DETAILS ON STUDY PROCEDURES

Please also refer to the Study Calendar in Section 7.

8.1 Screening Procedures

- **Informed Consent:** No protocol-related assessments may be performed prior to obtaining informed consent.
- **Medical History:** A complete relevant medical history should be obtained, including documentation of any clinically significant pre-existing conditions.
- **Physical Examination:** Evaluation by body system, including height, weight and neurologic exam to detect peripheral neuropathy.
- **Performance Status:** ECOG performance status
- **Vital Signs:** Vital signs should include temperature, heart rate, blood pressure and respiratory rate.
- **Cardiac Evaluation:** ECG and MUGA or ECHO
- **Laboratory Assessments:**
 - Serum chemistries: BUN, creatinine, (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
 - CBCD: complete blood count with differential and platelets
 - Serum pregnancy test for FCBP
 - HBV Serology: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody.
 - HBV DNA testing (by PCR): only for subjects positive for Anti-HBc or Anti-HBs
- **Baseline Symptoms and Toxicities:** Document pre-existing symptoms and any toxicities present (per NCI CTCAEv4.03) at the time of informed consent and prior to the first dose of study treatment
- **Concomitant Medications:** Document any concomitant medications; concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Disease Evaluation:**
 - Serum beta2-microglobulin
 - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD, IgE), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
 - Bone marrow aspirate and biopsy (see Section 8.8.3).
 - Skeletal Survey
 - Assess extramedullary plasmacytomas: PET/CT and/or Whole Body (WB)-MRI; performed for subjects with history of plasmacytomas or if clinically indicated

8.2 Induction Procedures

NOTE: The sections below are focused on study procedures, and not drug administration. Section 8.2.1 covers the non-laboratory assessments that are to be performed at each study visit.

NOTE: serum or urine pregnancy testing is required weekly only during cycle 1 of induction in FCBP. Thereafter it is required on day 1 of each cycle.

NOTE: Subjects with unknown HBV status not previously tested in screening and receiving carfilzomib should be tested for HBV as indicated in Section 7.

8.2.1 Throughout the Induction Period

- **AEs:** Record all AEs per the NCI CTCAEv4.03.
- **Concomitant Medications:** Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Disease Evaluation:**
 - Skeletal Survey (if clinically indicated)
 - Assess extramedullary plasmacytomas (if clinically indicated): PET/CT and/or WB-MRI

8.2.2 Day 1 Cycles 1-4 (unless otherwise noted)

- **Physical Exam:** Symptom-directed physical exam (to include weight). Subjects should also be monitored for second primary malignancies. If a subject's weight changes by more than 10% from induction C1D1, the dose of carfilzomib and elotuzumab should be re-calculated. This re-calculated weight should be used as the new baseline weight. For office visits required during the COVID-19 pandemic, virtual visits will be allowed per investigator discretion starting with Cycle 2 Day 1 induction.
- **Performance Status:** ECOG performance status. For required time-points during the COVID-19 pandemic, performance status may be performed virtually if the office visit is being performed virtually (starting with Cycle 2 Day 1 induction)
- **Vital Signs:** Vital signs should include temperature, heart rate, blood pressure and respiratory rate. Measure prior to elotuzumab infusion.
- **Cardiac Evaluation:** ECG
- **Laboratory Assessments**
 - Serum chemistries: BUN, creatinine, (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
 - CBCD: complete blood count with differential and platelets
 - Pregnancy test (serum or urine) in FCBP; **NOTE:** if screening pregnancy was done within 24 hours of C1D1 it does not to be repeated on C1D1.
- **Disease Evaluation:**
 - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD, IgE), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. Testing for IgD and IgE will only be performed for subjects with IgD and

IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects where a CR is suspected or maintained. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.

- **Blood sample for correlatives:** See Section 8.8.1.

8.2.3 Day 8, 15 and 22 Cycles 1-2 (unless otherwise noted)

- **Vital Signs:** Vital signs should include temperature, heart rate, blood pressure and respiratory rate. Measure prior to elotuzumab infusion. Cycles 1-2 only
- **Laboratory Assessments**
 - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
 - CBCD: complete blood count with differential and platelets
 - Pregnancy test (serum or urine) in FCBP: Cycle 1 only

8.3 Maintenance Procedures

NOTE: Subjects with unknown HBV status not previously tested in screening and receiving carfilzomib should be tested for HBV as indicated in Section 7.

8.3.1 Throughout the Maintenance Period

- **AEs:** Record all AEs per the NCI CTCAEv4.03.
- **Concomitant Medications:** Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.
- **Disease Evaluation:**
 - Skeletal Survey (if clinically indicated)
 - Assess extramedullary plasmacytomas (if clinically indicated): PET/CT and/or WB-MRI

8.3.2 Day 1 Cycles 1+ (unless otherwise noted)

- **Physical Exam:** Symptom-directed physical exam (to include weight). Subjects should also be monitored for second primary malignancies. If a subject's weight changes by more than 10% from induction C1D1, the dose of elotuzumab should be re-calculated. This re-calculated weight should be used as the new baseline weight. For office visits required during the COVID-19 pandemic, virtual visits will be allowed per investigator discretion.
- **Performance Status:** ECOG performance status. For required time-points during the COVID-19 pandemic, performance status may be performed virtually if the office visit is being performed virtually

- **Vital Signs:** Vital signs should include temperature, heart rate, blood pressure and respiratory rate. Measure prior to elotuzumab infusion.
- **Laboratory Assessments**
 - Serum chemistries: BUN, creatinine, (with calculated creatinine clearance on Day 1 of each cycle), glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
 - CBCD: complete blood count with differential and platelets
 - Pregnancy test (serum or urine) in FCBP.
- **Disease Evaluation:**
 - Blood and urine tests: Serum QIg (including IgA, IgM, IgG, IgD, IgE), SPEP, UPEP (24-hr urine sample required), serum and urine immunofixation, and serum FLC. Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma. Serum FLC to be performed for subjects with light chain only disease and for subjects where a CR is suspected or maintained. Subjects without measurable urine M-Protein at baseline will not be required to have UPEP or urine immunofixation repeated at subsequent disease assessment time-points, unless clinically indicated.
 - Bone marrow aspirate and biopsy (see Section 8.8.3): Collected post-induction (within 7 days prior to treatment on C1D1 of maintenance)
 - **Blood sample for correlatives:** C1D1, C3D1, and then every third maintenance cycle thereafter (C6, C9, etc) See Section 8.8.1.

8.3.3 Every 6 months for Cycles 1-n

- **Disease Evaluation:**
 - Bone marrow aspirate and biopsy (see Sections 7 and 8.8.3): Disease evaluation per standard of care

8.4 Time of CR

- **Disease Evaluation:**
 - Bone marrow aspirate and biopsy (see Section 8.8.3)
 - Assess extramedullary plasmacytomas: PET/CT and/or WB-MRI

8.5 Time of Disease Relapse/Progression

- **Disease Evaluation:**
 - Bone marrow aspirate and biopsy (see Section 8.8.3): At discretion of investigator
- **Blood sample for correlatives:** See Section 8.8.1.

8.6 Safety Follow-up Visit

This visit should occur in subjects 30 days (+/-10 days) after treatment stops for whatever reason (toxicity, progression, or at discretion of the investigator). **NOTE:** this 30-day time period applies even if the subject is taken off study treatment and begins new anti-cancer treatment during this time period.

- **Physical Exam:** Symptom-directed physical exam (to include weight). Subjects should also be monitored for second primary malignancies. For office visits required during the COVID-19 pandemic, virtual visits will be allowed per investigator discretion
- **Performance Status:** ECOG performance status. For required time-points during the COVID-19 pandemic, performance status may be performed virtually if the office visit is being performed virtually
- **Vital Signs:** Vital signs should include temperature, heart rate, blood pressure and respiratory rate.
- **Cardiac Evaluation:** ECG
- **Laboratory Assessments**
 - Serum chemistries: BUN, creatinine, glucose, uric acid, calcium, chloride, phosphorus, potassium, sodium, LDH, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, AST and ALT. **NOTE:** calcium should also be corrected for albumin.
 - CBCD: complete blood count with differential and platelets
- **AEs:** Record all AEs; subjects who have ongoing Grade 4 AE or SAE at the time of discontinuation from treatment, and those who come off treatment prematurely for safety reasons will continue to be followed until the event is resolved or deemed irreversible by the investigator.
- **Concomitant Medications:** Record any changes in concomitant medications. Concomitant medications include but are not limited to over the counter medications, supplements, and vitamins.

8.7 Follow-up

For subjects who discontinue study treatment before relapse or PD, disease evaluations should continue to be performed until relapse or confirmed PD, death, start of a new anticancer treatment, withdrawal of consent to study participation, or until the criteria for the final analysis are met (Section 14.5.1) whichever occurs first. The schedule for disease evaluation should follow the schedule outlined during maintenance. Survival follow-up will occur every 3 months (+/- 30 days) from the last administration of protocol-directed therapy until death, lost to follow-up, or until the criteria for the final analysis are met (Section 14.5.1) and may be conducted via telephone. Any second primary malignancies discovered during long-term follow-up will be documented. Follow-up clinical information may also be obtained through chart reviews or other data sources (e.g. death registries).

The investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated at another institution.

If the subject cannot be contacted following three attempted telephone calls over a period of 10 business days, the subject will be contacted in writing. Lost to follow-up is defined as four consecutive unsuccessful documented attempts (telephone and written) to contact the subject.

NOTE: in the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, subjects in follow-up will continue to be

followed until all subjects have discontinued study treatment and completed the Safety Follow-up Visit (see above).

8.8 Biospecimen Correlative Studies

8.8.1 Blood Samples for Correlative Studies

Blood (15mL) will be collected at each time-point for correlatives (characterization of immune cell subsets and flow cytometry) as outlined in the Study Calendar in Section 7. Comprehensive peripheral immune profiling techniques will be employed including:

- Soluble immune analytes measurements combining cytokine, chemokine and growth factor profiling [15 cytokines (IL-1b, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-9, IL-12p70, IL-13, IL-15, IL-17, IL-22, TNFa, INFg); 5 chemokines (IL-8, MIP1a, MIP1b, MCP1, IP10); and 5 growth factors (VEGF, FGF, PDGF, EGF, HGF) together with 3 markers of hypoxia and bone remodeling (IGF-1, HIF, RANK-L)].
- Flow cytometry-based enumeration and characterization of circulating effector and functional memory T cell mobilization (T helper and cytotoxic T cell subsets) [23] as well as $\gamma\delta$ T cells, NK cells, and inducible NK-T activation [23, 24].
- Circulating T cells ($\alpha\beta$ and $\gamma\delta$ subsets) clonal expansion assessment TCR-VD(J) rearrangement sequencing.
- Immunoseq[®] T cell clonal expansion measurement: DNA will be extracted from PBMCs for Immunoseq[®] sequencing of TCR's CRD3 region to be performed on a NGS Illumina[®] platform.

8.8.2 Blood Samples for Exploration of IRR

For subjects potentially experiencing grade ≥ 3 infusion-related adverse reaction (uniphasic or biphasic), we will conduct immune response analyses (with a particular emphasis on NK or T cell activation and polarization). In the event of a grade ≥ 3 IRR, every attempt will be made to draw a total of 15 mL of blood for immune response analyses, as soon as reasonably possible after the reaction if the subject is still in the infusion clinic.

8.8.3 Bone Marrow Samples

Bone marrow aspirates/biopsies will be collected at the time-points indicated in the Study Calendar in Section 7. In addition to routine clinical evaluation conducted on these samples (including flow cytometry, conventional cytogenetics and fluorescence in situ hybridization [FISH]), samples will also be evaluated for the following correlative studies:

- Flow cytometry-based tumor microenvironment analysis: MRD status will be assessed for this study in part using a flow cytometry-based MM MRD assay developed by the Euroflow consortium utilizing 10 markers (CD138, CD38, CD45, CD19, CD56, CD27, CD117, CD81, κ / λ free light chains) to identify plasma cells, differentiate normal from MM-PC and well as PC clonality. Using alternative gating strategy, this flow cytometry panel will also allow identification and characterization of NK, T, B and myeloid cell subsets.
- MRD assessment by NGS: MRD will be assessed via NGS which utilizes MM cell DNA from bone marrow samples.

- Micro-array / global gene expression analysis of isolated plasma cells.
- Clonal evolution of PC (and MM-PC subpopulation) IgG VJ rearrangement sequencing.
- Immunoseq[®] T cell clonal expansion measurement: DNA will be extracted from CD138- (plasma cell depleted) bone marrow fraction for Immunoseq[®] sequencing of TCR's CRD3 region to be performed on a NGS Illumina[®] platform.

In addition to the volumes required for routine clinical evaluation (if applicable), a minimum of 9mL of bone marrow aspirate (1st pull or 1st technical pull after needle repositioning) will be collected for MRD assessment by flow cytometry and NGS. An additional 10mL of bone marrow aspirate will be collected for CD138+ plasma cell isolation (B cell receptor sequencing).

8.8.4 Storage of Biospecimens

Any specimens remaining after biospecimen-based studies are complete will be stored in the Atrium Health (AH) Immune Monitoring Core Laboratory for follow-up/validation studies.

9. DISCONTINUATION FROM TREATMENT AND STUDY WITHDRAWAL

9.1 Treatment Discontinuation Criteria

Study treatment will continue until one of the following criteria applies:

- Disease relapse or progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Subject decides to withdraw study consent
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator
- Study subject becomes pregnant

NOTE: In the event the criteria for the final analysis are met, and there are subjects who have not yet been discontinued from study treatment, they will continue to receive therapy until one of the above criteria applies.

9.2 Off Study

When subjects are removed from the study, the reason for study removal and date the subject was removed should be documented. Reasons a subject may be removed from study include, but are not limited to:

- Subject non-compliance with study participation, in the opinion of the investigator
- The subject or legal representative (such as a parent or legal guardian) withdraws study consent
- The subject is lost to follow-up
- Study completion
- Investigator's decision to withdraw the subject

- Subject death.

Subjects that are Off Study will not participate in any study related procedures, including data collection.

10. DRUG INFORMATION

10.1 Elotuzumab

10.1.1 Supplier/How Supplied

Elotuzumab will be supplied free of charge to study subjects by the manufacturer, BMS as Elotuzumab for Injection, 400 mg/vials.

10.1.2 Preparation

The instructions will be found in the package insert and Investigator's Brochure.

10.1.3 Administration

See Section 6.4.2 for details.

10.1.4 Storage and Stability

The instructions will be found in the BMS Investigator's Brochure.

10.1.5 Handling

Elotuzumab should be handled using standard precautions for the safe handling of antineoplastic agents. Latex gloves are recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations, and stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study subjects.

10.1.6 Accountability

An adequate record of receipt, distribution, destruction, or return of this agent must be kept in the form of a Drug Accountability Form. The investigator, or responsible party designated by the investigator, will maintain a careful record of the inventory using the Drug Accountability Form. The investigational drug for this clinical trial shall only be dispensed by authorized personnel to subjects enrolled in this clinical trial.

10.1.7 Destruction

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from BMS, including the amount remaining at the conclusion of the trial. Upon completion or termination of the study, all unused product will be destroyed at the site as dictated by the manufacturer. Any vials that are used during dose preparation may be destroyed immediately after preparation. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.1.8 Drug Interactions

Elotuzumab is an IgG1 monoclonal antibody, which is likely eliminated via several pathways similar to that of other antibodies, and therefore, unlikely to be impacted by other drugs. However, PK analysis showed that the combination of lenalidomide/dexamethasone or bortezomib/dexamethasone with elotuzumab decreased nonspecific clearance of elotuzumab by approximately 35% and 50%, respectively, thus increasing steady-state exposure of elotuzumab compared to patients receiving elotuzumab monotherapy. The effect seen can mainly be attributed to dexamethasone, an immunosuppressant that can potentially affect antibody clearance (see IB for additional information).

10.1.9 Serious Adverse Reactions (SARs)

To identify expected SARs from clinical studies, BMS performed a cumulative review of reported adverse reactions from completed and ongoing studies for elotuzumab. The overall frequency includes reported serious, life-threatening, and fatal SARs. Frequency is defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) or uncommon ($\geq 1/1,000$ to $< 1/100$).

Serious Adverse Reactions for Elotuzumab Considered Expected

SAR	Frequency of all SARs	Occurrence of Life-Threatening SARs
Herpes zoster	Uncommon	No
Pneumonia	Common	No
Pneumonia Pneumococcal	Uncommon	No
Pyrexia	Common	No
Upper respiratory tract infection	Uncommon	No

Unexpected Life-Threatening and/or Fatal Serious Adverse Reactions with Elotuzumab

SARs	Frequency of Life-Threatening or Fatal SARs
Atrial Fibrillation	Uncommon
Atrioventricular block complete	Uncommon
Cardiac arrest	Uncommon
Brain abscess	Uncommon
Gastroenteritis	Uncommon
Influenza	Uncommon
Pneumocystis Jirovecii Pneumonia	Uncommon
Pneumonia	Uncommon
Pneumonia Fungal	Uncommon
Pulmonary Sepsis	Uncommon

Urinary Tract Infection	Uncommon
Urosepsis	Uncommon
Neutropenia	Uncommon
Thrombotic Thrombocytopenia Purpura	Uncommon
Sudden Death	Uncommon
Interstitial lung disease	Uncommon
Pulmonary embolism	Uncommon
Renal failure	Uncommon

The following warnings are associated with the use of elotuzumab (from the IB and/or the elotuzumab prescribing information):

- **IRR:** Elotuzumab can cause IRR, the most common symptoms of which include fever, chills and hypertension. Bradycardia and hypotension also developed during infusions. The majority of IRRs occur during the first dose. Premedication with dexamethasone, an H1 and H2 blocker and acetaminophen is required prior to each dose. See Section 6.4.4 for management of any IRR that occur during the study.
- **Infections:** The incidence of infections, including pneumonia, was higher with elotuzumab treatment than with control. In the largest clinical study of patients with multiple myeloma (N = 635, the ELOQUENT-2 trial described in Section 1.3.4.1, infections were reported in 81% of patients in the elotuzumab combined with lenalidomide and dexamethasone arm and 74% in the lenalidomide and dexamethasone arm. Grade 3 to 4 infections were noted in 28% and 24% of the elotuzumab+Rd and Rd arms, respectively. Fatal infections were infrequent and were reported in 2.5% of elotuzumab+Rd and 2.2% of Rd treated patients.
- **Second Primary Malignancies:** In ELOQUENT-2, invasive second primary malignancies have been observed in 9% of patients treated with elotuzumab+Rd and 6% of patients treated with Rd. Skin cancer was reported in 4.4% and 2.8% of patients treated with elotuzumab+Rd and Rd treated patients, respectively.
- **Hepatotoxicity:** Elevations in liver enzymes (aspartate transaminase/alanine transaminase [AST/ALT] >3X UNL, total bilirubin >2 x UNL, and alkaline phosphatase <2 xULN) consistent with hepatotoxicity were reported in 2.5% and 0.6% of elotuzumab+Rd and Rd treated patients, respectively in the ELOQUENT-2 trial. Two patients experiencing hepatotoxicity were not able to continue treatment; however, 6 out of 8 patients had resolution and were able to continue treatment.
- **Interference with Determination of Complete Response:** Elotuzumab is a humanized IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the determination of complete response and possibly relapse from complete response in patients with IgG kappa myeloma protein.

10.2 Carfilzomib

For complete information, please refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com.

Carfilzomib is proteasome inhibitor approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three prior lines of therapy, or as monotherapy in patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy.

10.2.1 Supplier/How Supplied

Commercial supplies of carfilzomib will be used and charged to the subject and or their insurance provider. Carfilzomib will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib.

10.2.2 Reconstitution and Preparation

Refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com, for instructions on reconstitution and preparation of carfilzomib.

10.2.3 Storage and Stability

Refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com, for details on stability of unopened vials of carfilzomib, and on stability of carfilzomib once it is reconstituted.

10.2.4 Handling

Carfilzomib should be handled using standard precautions for the safe handling of antineoplastic agents. Latex gloves are recommended. It must be dispensed only from official study sites by authorized personnel according to local regulations, and stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that study drug is only dispensed to eligible study subjects.

10.2.5 Adverse Events Associated with Carfilzomib

For complete information on safety, please refer to the latest version of the prescribing information for carfilzomib, which can be found at www.kyprolis.com.

The safety of carfilzomib in combination with lenalidomide and dexamethasone (KRd) was evaluated in an open-label randomized study in patients with relapsed multiple myeloma. Adverse Reactions that occurred at a rate of $\geq 10\%$ in the KRd arm (n=392) during the first 12 cycles of therapy are in the table below.

Adverse Reaction	KRd Arm n (%)	
	Any Grade	\geq Grade 3
Anemia	138 (35)	53 (14)
Asthenia	54 (14)	11 (3)

Back Pain	41 (11)	4 (1)
Bronchitis	55 (14)	5 (1)
Constipation	68 (17)	0
Cough	93 (24)	2 (1)
Diarrhea	119 (30)	8 (2)
Dyspnea	71 (18)	8 (2)
Fatigue	113 (29)	23 (6)
Hyperglycemia	43 (11)	18 (5)
Hypertension	41 (11)	12 (3)
Hypocalcemia	55 (14)	10 (3)
Hypokalemia	78 (20)	22 (6)
Insomnia	64 (16)	6 (2)
Muscle spasms	92 (24)	3 (1)
Nausea	63 (16)	1 (0)
Neutropenia	124 (32)	104 (27)
Peripheral edema	59 (15)	3 (1)
Peripheral neuropathies	43 (11)	7 (2)
Pneumonia	54 (14)	35 (9)
Pyrexia	93 (24)	5 (1)
Rash	45 (12)	5 (1)
Thrombocytopenia	100 (26)	58 (15)
Upper Respiratory Tract Infection	87 (22)	7 (2)
Venous Embolic and Thrombotic Events	49 (13)	16 (4)
Viral upper respiratory tract infection	55 (14)	0

Laboratory abnormalities \geq Grade 3 reported at a rate of \geq 10% in the KRd arm included decreases in the following (% of patients): lymphocytes (46%), ANC (39%), phosphorus (31%), platelets (26%), total WBC (25%), hemoglobin (15%) and potassium (11%). Increased glucose (14%) was also reported.

The following warnings are associated with the use of carfilzomib (from the August 2020 prescribing information):

- Cardiac Toxicities:** New onset or worsening of pre-existing cardiac failure (e.g., congestive heart failure, pulmonary edema, decreased ejection fraction), restrictive cardiomyopathy, myocardial ischemia, and myocardial infarction including fatalities have occurred following administration of carfilzomib. Some events occurred in patients with normal baseline ventricular function. In clinical studies with carfilzomib, these events occurred throughout the course of carfilzomib therapy. Death due to cardiac arrest has occurred within one day of carfilzomib administration. In randomized, open-label, multicenter trials for combination therapies, the incidence of cardiac failure events was 8% and that of arrhythmias was 8% (majority of which were atrial fibrillation and sinus tachycardia). In patients \geq 75 years of age, the risk of cardiac failure is increased compared to younger patients.

- **Acute Renal Failure:** Cases of acute renal failure have occurred in patients receiving carfilzomib. Some of these events have been fatal. Renal insufficiency adverse events (including renal failure) have occurred in approximately 9% of patients treated with carfilzomib. Acute renal failure was reported more frequently in patients with advanced relapsed and refractory multiple myeloma who received carfilzomib monotherapy. This risk was greater in patients with a baseline reduced estimated creatinine clearance (calculated using Cockcroft and Gault equation).
- **Tumor Lysis Syndrome:** Cases of TLS, including fatal outcomes, have been reported in patients who received carfilzomib. Patients with multiple myeloma and a high tumor burden should be considered to be at greater risk for TLS.
- **Pulmonary Toxicity:** Acute Respiratory Distress Syndrome (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease such as pneumonitis and interstitial lung disease have occurred in approximately 2% of patients receiving carfilzomib. Some events have been fatal.
- **Pulmonary Hypertension:** Pulmonary arterial hypertension was reported in approximately 2% of patients treated with carfilzomib and was \geq Grade 3 in less than 1% of patients.
- **Dyspnea:** Dyspnea was reported in 25% of patients treated with carfilzomib and was \geq Grade 3 in 4% of patients. Evaluate dyspnea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes.
- **Hypertension:** Hypertension, including hypertensive crisis and hypertensive emergency, has been observed with carfilzomib. In a randomized, open-label, multicenter trial evaluating carfilzomib in combination with KRd *versus* Rd, the incidence of hypertension events was 17% in the KRd arm *versus* 9% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of hypertension events was 34% in the Kd arm *versus* 11% in the Vd arm. Some of these events have been fatal. Monitor blood pressure regularly in all patients.
- **Venous Thrombosis:** Venous thromboembolic events (including deep venous thrombosis and pulmonary embolism) have been observed with carfilzomib. In a randomized, open-label, multicenter trial evaluating KRd *versus* Rd (with thromboprophylaxis used in both arms), the incidence of venous thromboembolic events in the first 12 cycles was 13% in the KRd arm *versus* 6% in the Rd arm. In a randomized, open-label, multicenter trial of Kd *versus* Vd, the incidence of venous thromboembolic events in months 1–6 was 9% in the Kd arm *versus* 2% in the Vd arm. With carfilzomib monotherapy, the incidence of venous thromboembolic events was 2%.
- **Infusion Reactions:** Infusion reactions including life-threatening reactions, have occurred in patients receiving carfilzomib. Symptoms include fever, chills, arthralgia, myalgia, facial flushing, facial edema, laryngeal edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib.
- **Hemorrhage:** Fatal or serious cases of hemorrhage have been reported in patients treated with carfilzomib. Hemorrhagic events have included gastrointestinal, pulmonary, and intracranial hemorrhage and epistaxis. The bleeding can be spontaneous, and intracranial hemorrhage has occurred without trauma. Hemorrhage has been reported in patients having either low or normal platelet counts. Hemorrhage has also been reported in patients who were not on antiplatelet therapy or anticoagulation.

- **Thrombocytopenia:** Carfilzomib causes thrombocytopenia with platelet nadirs observed between Day 8 and Day 15 of each 28-day cycle, with recovery to baseline platelet count usually by the start of the next cycle. Thrombocytopenia was reported in approximately 32% of patients in clinical trials with carfilzomib.
- **Hepatic Toxicity and Hepatic Failure:** Cases of hepatic failure, including fatal cases, have been reported (2%) during treatment with carfilzomib. Carfilzomib can cause increased serum transaminases.
- **Thrombotic Microangiopathy:** Cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), have been reported in patients who received carfilzomib. Some of these events have been fatal. Monitor for signs and symptoms of TTP/HUS. If the diagnosis is suspected, stop carfilzomib and evaluate. If the diagnosis of TTP/HUS is excluded, carfilzomib may be restarted. The safety of reinitiating carfilzomib therapy in patients previously experiencing TTP/HUS is not known.
- **Posterior Reversible Encephalopathy Syndrome:** Cases of posterior reversible encephalopathy syndrome (PRES) have been reported in patients receiving carfilzomib. PRES, formerly termed Reversible Posterior Leukoencephalopathy Syndrome (RPLS), is a neurological disorder which can present with seizure, headache, lethargy, confusion, blindness, altered consciousness, and other visual and neurological disturbances, along with hypertension, and the diagnosis is confirmed by neuro-radiological imaging (MRI). Discontinue carfilzomib if PRES is suspected and evaluate. The safety of reinitiating carfilzomib therapy in patients previously experiencing PRES is not known.
- **Progressive Multifocal Leukoencephalopathy (PML):** Progressive multifocal leukoencephalopathy (PML), which can be fatal, has been reported with Kyprolis. In addition to Kyprolis, other possible contributory factors include prior or concurrent immunosuppressive therapy that may cause immunosuppression. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue Kyprolis and initiate evaluation for PML including neurology consultation.
- **HBV Reactivation:** Cases of HBV reactivation have been reported in the clinical trial and post-marketing setting in patients receiving treatment with carfilzomib. Subjects should be tested for HBV infection before initiating treatment with carfilzomib. Subjects who are currently receiving treatment with carfilzomib and with unknown HBV status should be also be tested for HBV infection. For subjects who are carriers of HBV, prophylaxis with antivirals should be considered. Carriers of HBV who require treatment with carfilzomib should be closely monitored for signs and symptoms of active HBV infection throughout and following the end of treatment with carfilzomib. Consider consulting a specialist for subjects who test positive for HBV prior to or during treatment with carfilzomib. For subjects with active HBV reactivation, carfilzomib should be withheld until infection is adequately controlled. The safety of resuming carfilzomib after HBV reactivation is adequately controlled is not known. Therefore, investigators should weigh the risks and benefits when considering resumption of therapy in this situation.
- **Increased Fatal and Serious Toxicities in Combination with Melphalan and Prednisone in Newly Diagnosed Transplant-Ineligible Patients:** In a clinical trial of 955 transplant-ineligible patients with newly diagnosed multiple myeloma randomized to carfilzomib (20/36 mg/m² by 30-minute infusion twice weekly for four of each six-week

cycle), melphalan and prednisone (KMP) or bortezomib, melphalan and prednisone (VMP), a higher incidence of fatal adverse reactions (7% versus 4%) and serious adverse reactions (50% versus 42%) were observed in the KMP arm compared to patients in the VMP arm, respectively. Patients in the KMP arm were observed to have a higher incidence of any grade adverse reactions involving cardiac failure (11% versus 4%), hypertension (25% versus 8%), acute renal failure (14% versus 6%), and dyspnea (18% versus 9%). This study did not meet its primary outcome measure of superiority in progression-free survival for the KMP arm. Carfilzomib in combination with melphalan and prednisone is not indicated for transplant-ineligible patients with newly diagnosed multiple myeloma

- **Embryo-fetal Toxicity:** Carfilzomib can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. Carfilzomib administered intravenously to pregnant rabbits during organogenesis at a dose approximately 40% of the clinical dose of 27 mg/m² based on body surface area caused post-implantation loss and a decrease in fetal weight. Females of reproductive potential should avoid becoming pregnant while being treated with carfilzomib and must use contraception during treatment and for 6 months following the final dose. Males with female sexual partners of reproductive potential must use contraception during treatment with carfilzomib and for 3 months following the final dose.

10.3 Lenalidomide

For complete information, please refer to the latest version of the prescribing information for lenalidomide, which can be found at www.revlimid.com.

Lenalidomide is a thalidomide analogue approved by the FDA in combination with dexamethasone for the treatment of patients with MM, and for use as maintenance therapy post ASCT.

10.3.1 Supplier/How Supplied

Commercial supplies of lenalidomide will be used and charged to the subject and or their insurance provider. However, subjects in the U.S. must be enrolled into the REVLIMID Risk Evaluation and Mitigation Strategy (REMS)TM program for the procurement of lenalidomide. Lenalidomide is formulated in hard capsules containing 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, or 25 mg active drug for PO administration only.

10.3.2 Storage and Stability

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

10.3.3 Handling

Lenalidomide should be handled using standard precautions for the safe handling of antineoplastic agents. Latex gloves are recommended. Lenalidomide capsules should not be opened or broken.

10.3.4 Adverse Events Associated with Lenalidomide

For complete information on safety, please refer to the latest version of the prescribing information for lenalidomide, which can be found at www.revlimid.com. The most common adverse reactions ($\geq 20\%$) when lenalidomide is used in MM include diarrhea, fatigue, anemia, constipation, neutropenia, leukopenia, peripheral edema, insomnia, muscle cramp/spasms, abdominal pain, back pain, nausea, asthenia, pyrexia, upper respiratory tract infection, bronchitis, nasopharyngitis, gastroenteritis, cough, rash, dyspnea, dizziness, decreased appetite, thrombocytopenia and tremor.

The following warnings are associated with the use of lenalidomide **in MM**:

- **BLACK BOX WARNING: Embryo-fetal Toxicity:** Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Because of this, lenalidomide is only available through a restricted distribution program called the REVLIMID REMS™ program.
- **BLACK BOX WARNING: Hematologic Toxicity:** Lenalidomide can cause significant neutropenia and thrombocytopenia.
- **BLACK BOX WARNING: Venous and Arterial Thromboembolism:** There is a significantly increased risk of venous thromboembolic events (deep vein thrombosis and pulmonary embolism), as well as risk of arterial thromboembolic events (ATE, myocardial infarction and stroke) in patients with MM receiving lenalidomide in combination with dexamethasone. Anti-thrombotic prophylaxis is recommended.
- **Second Primary Malignancies:** In clinical trials in patients with MM receiving lenalidomide an increase of invasive second primary malignancies notably AML and MDS have been observed. The increase of cases of AML and MDS occurred predominantly in NDMM patients receiving lenalidomide in combination with oral melphalan (frequency of 5.3%) or immediately following high dose intravenous melphalan and ASCT (frequency of 7.5%).
- **Increased Mortality in Patients with MM When Pembrolizumab Is Added to a Thalidomide Analogue and Dexamethasone:** In two randomized clinical trials in patients with MM, the addition of pembrolizumab to a thalidomide analogue plus dexamethasone, a use for which no PD-1 or PD-L1 blocking antibody is indicated, resulted in increased mortality. Treatment of patients with MM with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.
- **Hepatotoxicity:** Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatotoxicity (with hepatocellular, cholestatic and mixed characteristics); 2% of patients with MM and 1% of patients with myelodysplasia had serious hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors.
- **Severe Cutaneous Reactions Including Hypersensitivity Reactions:** Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS), toxic

epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported. DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. These events can be fatal.

- **Tumor Lysis Syndrome:** Fatal instances of TLS have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment.
- **Impaired Stem Cell mobilization:** A decrease in the number of CD34+ cells collected after treatment (> 4 cycles) with lenalidomide has been reported.
- **Thyroid Disorders:** Both hypothyroidism and hyperthyroidism have been reported.
- **Hypersensitivity:** Hypersensitivity, including angioedema, anaphylaxis, and anaphylactic reactions to lenalidomide has been reported.

10.4 Dexamethasone

Dexamethasone is a synthetic adrenoglucocorticoid. It is commercially available as a generic in tablet form for oral administration. It is indicated for a variety of medical conditions, including cancer. Commercial supplies of dexamethasone will be used for this study and charged to study subjects or their insurance company.

10.4.1 Storage

Dexamethasone is to be stored at controlled room temperature 20 to 25°C (68 to 77°F). Consult the package insert of the respective product for additional storage and usage instructions.

10.4.2 Summary of Adverse Events Associated with Dexamethasone

See Reference [25] for a more complete summary. Also see Section 6.6.2, Table 14.

The side effects from systemic glucocorticoids are usually dose and duration dependent, and can impact virtually all body systems. Common side effects include thinning of the skin, purpura, Cushingoid appearance, weight gain, sleep disturbance and mood changes. Hyperglycemia is common if these agents are used in patients with pre-existing diabetes or those at risk of diabetes for other reasons. Cataracts are also common with prolonged (>1 year) of glucocorticoids. Other risks of concern with glucocorticoids include an increased risk of cardiovascular disease and hypertension (particularly when glucocorticoids are prescribed in patients with pre-existing cardiac or renal disease), increased risk of peptic ulcer disease and gastritis (especially when patients are also taking nonsteroidal anti-inflammatory agents), osteoporosis, increased fracture risk, osteonecrosis, myopathy, edema, and immunosuppression with an increased risk of infection. With the exception of cataracts and some of the cardiac and bone toxicities, adverse effects from glucocorticoids are at least partially reversible upon discontinuation.

11. DATA AND SAFETY MONITORING PLANS

11.1 Safety Monitoring

This protocol will be monitored according to the processes in effect for all LCI investigator-initiated studies and the protocol-specific monitoring plan, and will abide by standard operating procedures (SOPs) set forth by both AH Office of Clinical and Translational Research and the LCI Clinical Trials Office. It is the responsibility of the Sponsor-Investigator to monitor the safety data for this study. The Sponsor-Investigator, Statistician, and other team members as needed will meet regularly to monitor subject consents, enrollment and retention, safety data for all subjects (including AEs for all grades and attributions, SAEs), study drug administration, and validity/integrity of the data. Documentation of these meetings will be kept with study records. The Sponsor-Investigator will submit data to the LCI Data and Safety Monitoring Committee according to the protocol-specific Data and Safety Monitoring Plan.

The Sponsor-Investigator will monitor the study accrual data regularly.

11.2 Data Monitoring

This study will be organized, performed, and reported in compliance with the study protocol, SOPs of the LCI and AH Office of Clinical and Translational Research (and/or other participating institutional SOPs), the FDA, and other applicable regulations and guidelines (e.g. GCP).

Subjects will be monitored by LCI Research /Data Monitors per the study-specific monitoring plan and LCI/AH SOPs for data quality. This monitoring will be done by comparing source documentation to the electronic case report forms (eCRFs). Any variation between the two data sets will be discussed with the investigator, Sponsor-Investigator and/or other study team members as appropriate.

The study database will be reviewed and checked for omissions, apparent errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be generated and addressed by the appropriate study team member. Only authorized personnel will make corrections to the study database and all corrections will be documented in an electronic audit trail.

The trial site may also be subject to quality assurance audit by BMS or its designee as well as inspection by appropriate regulatory agencies.

It is important for all investigators and their relevant personnel to be available during the monitoring visits and possible audits and for sufficient time to be devoted to the process.

12. SAFETY DATA COLLECTION, RECORDING AND REPORTING

12.1 Definitions

12.1.1 Adverse Event

An adverse event is any untoward medical occurrence in a study subject who is administered any drug that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions that increase in frequency or severity or change in nature during or as a consequence of use of a drug in human clinical trials are also considered adverse events. Adverse events may also include pre- or post-treatment complications that occur as a result of protocol mandated procedures (e.g., invasive procedures such as biopsies).

An increase in grade to a pre-existing CTCAE toxicity grade present at the time of study treatment initiation will be recorded as an AE. Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE if they are judged clinically significant by the investigator and/or require a medical intervention or dose modification.

Any continuing medical condition or clinically significant laboratory abnormality with an onset date before the first date of study treatment administration should be considered pre-existing and should be documented.

An AE does not include:

- relapse or progression of the underlying malignant disease;
- medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion);
NOTE: the condition that leads to the procedure may be an adverse event;
- situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions);

The severity of adverse events should be classified and recorded according to the CTCAE version 4.03.

12.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant

drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the Sponsor-Investigator could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

12.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

12.1.4 Serious AE or SAR

An AE or SAR is to be considered serious if the investigator deems it as such and the event results in any of the following outcomes:

- Death (fatal);
- Life-threatening situation (subject is at immediate risk of death);
- Persistent or significant disability/incapacity;
- Requires or prolongs inpatient hospitalization¹;
- A congenital anomaly/birth defect in the offspring of a subject who received study drug;
- Based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the afore listed outcomes from occurring (e.g. intensive treatment in an emergency room without hospitalization, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse). **NOTE:** Potential drug induced liver injury (DILI²) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy³, overdose⁴, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

¹Hospitalizations for study drug administration, protocol-related procedures, palliative or hospice care, or placement of an indwelling catheter, unless associated with other serious events, will not be recorded as SAEs. Other hospitalizations planned at the beginning of the trial also do not need to be reported as an SAE.

²Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential

DILIs, meeting the defined criteria below must be reported as SAEs. Potential DILI is defined as

1. ALT or AST elevation > 3 X ULN **AND**
2. Total bilirubin > 2 X ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) **AND**
3. No other immediately apparent possible causes of AST/ALT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

³Pregnancy

If, following initiation of study treatment, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study treatment exposure, including during at least 5 half-lives after product administration, the pregnancy must be reported as an SAE.

⁴Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

12.1.5 Unexpected AE (AE or SAE) or SAR

An AE or SAR (whether serious or not) is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., IB for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.1.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

12.1.7 Unanticipated Problem (UAP)

An UAP is any incidence, experience or outcome that is unexpected, given the information provided in research-related documentation (e.g., IB, informed consent) and the study population characteristics that is related or possibly related to participation in the research study and places the participant at an increased risk. By this definition, any event that meets the criteria defined in Section 12.1.5 would meet the criteria for a UAP. However other events may also meet the criteria for a UAP, e.g., a lost or stolen laptop computer that contains sensitive study information.

12.2 Attribution

The relationship to study treatment should be assessed using the following definitions:

Definite	The AE is <i>clearly related</i> to the drug(s) under investigation
Probable	The AE is <i>likely related</i> to the drug(s) under investigation
Possible	The AE <i>possibly related</i> to the drug(s) under investigation
Unlikely	The AE is <i>doubtfully related</i> to the drug(s) under investigation
Unrelated	The AE is <i>clearly not related</i> to the drug(s) under investigation

The investigator is responsible for verifying and providing source documentation for all AEs and assigning the attribution for each event for all subjects enrolled on the trial.

12.3 Timing and Reporting

12.3.1 Adverse Events

All AEs, (including event name, grade, start/stop date and attribution) will be documented. AEs will be collected from the time of D1 of treatment until 90 days after last dose of study treatment. If the subject initiates subsequent anti-cancer therapy prior to 90 days after cessation of study treatment, the reporting period is through 30 days following cessation of study treatment or until the start of the subsequent anti-cancer therapy, whichever is later.

12.3.2 Pregnancy

All initial reports of pregnancy must be reported as an SAE to BMS Worldwide Safety (see Section 12.3.3.2) by the Sponsor-Investigator or designee within 24 hours of becoming aware of the event using the BMS Pregnancy Surveillance Form (provided as a document separate from this protocol). Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered SAEs and must be reported as such.

Any subject who becomes pregnant during the study must be discontinued promptly from all protocol mandated treatment and followed up per protocol.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS].

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

12.3.3 SAEs

All SAEs, whether related to study treatment or not, including those thought to be associated with protocol-specified procedures, will be collected. SAEs will be reported after informed consent and continuing through 90 days after the discontinuation of all protocol mandated therapy. If the subject initiates subsequent anti-cancer therapy prior to 90 days after cessation of study treatment, the reporting period is through 60 days following cessation of study treatment or until the start of the subsequent anti-cancer therapy, whichever is later. Any SAE occurring after these time periods that is believed to be related to study drug(s) or protocol-specified procedure should also be reported.

It is the responsibility of the Sponsor-Investigator, investigators and the protocol team to ensure SAEs are reported according to the Code of Federal Regulations (CFR), GCP, the protocol guidelines, IRB, and FDA policy.

SAEs will be followed until clinical recovery is complete and laboratory tests have returned to baseline, until progression has been stabilized, or until there has been acceptable resolution of the event. This may at times cause the follow-up period for SAEs to be greater than 90 days. Similarly, the Sponsor-Investigator is responsible for following the subject during the required follow-up period even if the subject lives elsewhere or has been released from his or her care and is being treated under another service at LCI.

12.3.3.1 Reporting to Sponsor-Investigator

All SAEs (whether considered related or not, expected or not) and pregnancies must be reported to the Sponsor-Investigator within 1 business day of awareness.

When new significant information becomes available, a follow-up report must be reported to the Sponsor-Investigator within 1 business day of awareness.

In the event of an unanticipated problem (UAP) as defined in Section 12.1.7 or life-threatening complication the Sponsor-Investigator must be notified via email immediately after awareness.

12.3.3.2 Reporting to BMS Worldwide Safety

All SAEs whether considered related or not, expected or not, and pregnancies must be reported to BMS within 24 hours of Sponsor-Investigator awareness. SAEs are reportable to BMS from informed consent through 60 days after last dose of study treatment. SAEs must be recorded on a BMS approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

NOTE: if a report is submitted to the FDA (see Section 12.3.5), a simultaneous copy should be submitted to BMS.

12.3.4 Reporting to the IRB

All events occurring during the conduct of a protocol and meeting the definition of an SAE or UAP will be reported to the IRB per IRB reporting requirements.

12.3.5 Reporting to the FDA

According to CFR 312.32, the Sponsor-Investigator, or designee, will be responsible for notifying the FDA (via Form FDA 3500 (MedWatch Form)) and all participating investigators of any **unexpected fatal or life-threatening events** possibly related with the use of the study drug (drugs) as soon as possible, but in no case later than 7 calendar days after the Sponsor's initial receipt of the information. For all other serious and unexpected safety events, the Sponsor-Investigator, or designee, will notify the FDA within 15 calendar days.

It is the responsibility of the Sponsor-Investigator, investigators, and the Protocol Team to ensure SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, Institutional Review Board, and FDA policy.

13. DISEASE EVALUATION

13.1 IMWG 2016 Response Criteria

Response	IMWG Criteria*
Abbreviations: NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anemia, lytic bone lesions. FCM=flow cytometry. SUVmax=maximum standardised uptake value. MFC=multiparameter flow cytometry. ¹⁸ F-FDG PET= ¹⁸ F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.	
IMWG MRD Criteria (Requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years)†

Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10 ⁵ nucleated cells § or higher
Imaging-positive MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue ¶
Standard IMWG Response Criteria ; NOTE: see [22, 30 & 31] for additional details	
Stringent Complete Response (sCR)	CR as defined below plus: <ul style="list-style-type: none"> • normal FLC ratio ** and • absence of clonal cells in bone marrow by immunohistochemistry(κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete Response (CR)	<ul style="list-style-type: none"> • Negative immunofixation on the serum and urine ‡‡ and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow aspirates.
Very Good Partial Response (VGPR)	<ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h.
Partial Response (PR)	<ul style="list-style-type: none"> • ≥ 50% reduction of serum M-protein plus reduction in 24 hour urinary M-protein by ≥ 90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD) §§of soft tissue plasmacytomas is also required
Minimal Response	<ul style="list-style-type: none"> • ≥25% but ≤49% reduction of serum M-protein and • reduction in 24-h urine M-protein by 50–89%. <p>In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required</p>
Stable Disease (SD)	<ul style="list-style-type: none"> • Not meeting criteria for CR, VGPR, PR, minimal response, or PD
Progressive disease (PD)¶¶,	Any one or more of the following criteria: <ul style="list-style-type: none"> • Increase of 25% from lowest confirmed response value in one or more of the following criteria:

	<ul style="list-style-type: none"> ○ Serum M-protein (absolute increase must be ≥ 0.5 g/dL) ○ Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; ○ Urine M-protein (absolute increase must be ≥ 200 mg/24 h); ○ In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels. (absolute increase must be > 10 mg/dL); ○ In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be $\geq 10\%$) ○ Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD§§ of >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion >1 cm in short axis; ○ $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease=
Clinical Relapse	<p>Clinical relapse requires one or more of the following criteria:</p> <ul style="list-style-type: none"> • Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of TTP or PFS but is listed as something that can be reported optionally or for use in clinical practice • Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD§§ of the measurable lesion • Hypercalcaemia (>11 mg/dL) • Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions • Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; • Hyperviscosity related to serum paraprotein
<p>For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid hemodilution.</p> <p>*All response categories require two consecutive assessments made at any time before the institution of any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g. after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions or extra medullary plasmacytomas if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.</p> <p>†Sustained MRD negativity when reported should also annotate the method used (e.g. sustained flow MRD-negative, sustained sequencing MRD-negative).</p> <p>‡Bone marrow MFC should follow NGF guidelines²⁶. The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available</p>	

globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequentia).

¶Criteria used by Zamagni and colleagues²⁷ and expert panel (IMPetUs; Italian Myeloma criteria for PET Use)^{28,29}. Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an $SUV_{max}=2.5$ within osteolytic CT areas >1 cm in size, or $SUV_{max}=1.5$ within osteolytic CT areas ≤ 1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

||Derived from international uniform response criteria for multiple myeloma.³⁰ Minor response definition and clarifications derived from Rajkumar and colleagues³¹. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a $\geq 90\%$ decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

**All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

††Presence/absence of clonal cells on immunohistochemistry is based upon the $\kappa/\lambda/L$ ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of $>4:1$ or $<1:2$.

‡‡Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

¶¶Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

||||In the case where a value is felt to be a spurious result per physician discretion (e.g. a possible laboratory error), that value will not be considered when determining the lowest value.

14. STATISTICAL CONSIDERATIONS

14.1 Milestones

14.1.1 Registration Date

The date the subject signs the informed consent.

14.1.2 Enrollment (On Study) Date

The date of initiation of study treatment on Cycle 1, Day 1.

14.1.3 Treatment Discontinuation Date

The date the investigator makes the decision to discontinue elotuzumab. See Section 9 for criteria for discontinuation of treatment.

14.2 Sample Size Determination

The primary objective of this study is to evaluate the very good partial response or better (VGPR+) rate in subjects treated with elotuzumab in addition to the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) in relapsed or refractory multiple myeloma subjects. This will be evaluated in terms of the percent of subjects who achieve a VGPR+ to induction therapy. Wang [6] reported a VGPR+ rate of approximately 40% in this patient population treated with KRd. See Section 1.4 for the rationale for using this as the historical control. This study will be used to test the null hypothesis that the VGPR+ rate in subjects treated with elotuzumab+KRd is less than or equal to 40%. Forty (40) response evaluable subjects will be enrolled, and if at least 21 of 40 subjects achieve a VGPR+, the null hypothesis will be rejected. The design will provide 90% power with a 1-sided alpha = 0.10 significance level, assuming the true VGPR+ rate is 60%. An improvement from 40% to 60% in the VGPR+ rate is considered clinically relevant.

14.3 Endpoint Definitions

14.3.1 Very Good Partial Response or Better

VGPR+ will be determined for each subject as a binary variable indicating whether or not the subject achieved a VGPR or better to induction, as determined by the IMWG 2016 response criteria (see Section 13.1).

14.3.2 Objective Response

Objective response will be determined for each subject as a binary variable indicating whether or not the subject achieved a best overall response of PR or better as determined by the IMWG 2016 response criteria.

14.3.3 Overall Survival

Overall survival (OS) is defined as the duration from enrollment to the study (treatment start date) to the date of death from any cause. Subjects who are alive or lost to follow-up at the time of the analysis will be censored at the last known date they were alive.

14.3.4 Progression Free Survival

Progression free survival (PFS) is defined as the duration of time from enrollment to the study (treatment start date) to first occurrence of either PD or death. Disease progression must be objectively determined per IMWG 2016 criteria (see Section 13.1), where the date of progression is the date of the last assessment that identified PD. If the subject died without documented disease progression, the date of progression will be the date of death. For surviving subjects who do not have documented disease progression, PFS will be censored at the date of last disease assessment. For subjects who receive subsequent anti-cancer therapy prior to documented disease progression, PFS will be censored at the date of last disease assessment prior to the commencement of subsequent therapy. Subjects who have an initial PFS event immediately following 2 or more consecutive missed disease assessments will be censored at the date of the last assessment prior to those missed assessments. For participants with only one missed assessment, the documented PD status and assessment date will be used.

14.3.5 Time to Disease Progression

Time to disease progression (TTP) will be calculated in the same fashion as described for PFS with the exception that for subjects who die for causes other than disease progression, TTP will be censored at the date of the other cause mortality. Otherwise, the censoring mechanism for TTP will be the same as previously described for PFS.

14.3.6 Duration of Response

Duration of response (DoR) will be calculated for each subject with response for the VGPR+ and overall response endpoints. The DoR intervals will be calculated from the time of the first assessment that identified response until disease progression or death. The censoring mechanism for DoR will be the same as described for PFS.

14.3.7 Time to Next Treatment

Time to next treatment (TTNT) will be calculated from the time of treatment start until the start of the first subsequent anti-cancer therapy after all protocol directed therapy is completed. For surviving subjects who do not receive subsequent therapy, TTNT will be censored at the last contact date. For subjects who die before beginning subsequent anti-cancer therapy, TTNT will be censored at the date of death.

14.3.8 Safety Endpoints

Safety endpoints will include treatment administration (cumulative dose, dose intensity, and relative dose intensity—dose intensity as a percent of intended dose intensity), AEs, SAEs, and deaths while on study therapy.

14.4 Analysis Populations

Analyses of response endpoints (response evaluable population) will be conducted on the population of subjects who initiate treatment with elotuzumab and who have measurable disease at baseline. Analyses of other efficacy and safety endpoints will be conducted on the population of subjects who initiate treatment with elotuzumab. Exploratory analyses will be conducted on the population of subjects who initiate treatment with elotuzumab treatment and who have available biomarker data.

14.5 Analysis Methods

14.5.1 Timing of Analysis

The primary analysis will occur after VGPR+ status (yes or no) has been determined for all subjects. Secondary endpoints will also be assessed at the time of the primary analyses. Updated analyses will be conducted after the PFS censoring rate reaches 20% or when all surviving subjects who are not lost to follow up or have not been withdrawn from the study have been on study for at least 3 years, whichever occurs first. A final analysis will be conducted after the overall survival censoring rate reaches 20% or after all surviving subjects who are not lost to follow up or have not been withdrawn from the study have been on study for at least 5 years, whichever occurs first.

14.5.2 Subject Disposition

A disposition summary of all consenting subjects will be provided. This will include a summary of subjects who consented, were treated, discontinued treatment, died, and were lost to follow-up or withdrew consent.

14.5.3 Baseline Subject and Disease Characteristics

A summary of subject demographics and disease-related characteristics will be summarized and evaluated. These results will be qualitatively compared to patient and disease characteristics in the same patient population that have been previously reported.

14.5.4 Primary Analysis

The frequency and proportion of subjects experiencing a VGPR+ will be calculated. A corresponding 95% confidence interval will be estimated using the Clopper-Pearson method. A one-sided test for binomial proportions using the rejection region described in the sample size section (Section 14.2) will be carried out, testing the null hypothesis that the VGPR+ rate is less than or equal to 40%. Based on the design and corresponding sample size calculations described in Section 14.2, if at least 21 subjects experience a VGPR+, the null hypothesis can be rejected.

Logistic regression techniques will be used to correlate VGRR+ rate with baseline subject and disease characteristics, and results from biomarker studies as previously described. This will include univariate and multivariable regression model techniques to identify individual and independent prognostic factors.

14.5.5 Secondary Analysis

The frequencies and proportions of overall response will be calculated. Corresponding 95% confidence intervals will be estimated using the Clopper-Pearson method. OS, PFS, TTP, TTNT, and DoR endpoints will be analyzed using Kaplan Meier techniques. Selected landmarks will be estimated and reported. Logistic regression models and Cox proportional hazards models will be used to analyze the treatment response endpoints as functions of baseline subject and disease characteristics, and results from biomarker studies as previously described. The percent of subjects achieving MRD negative status will be summarized. Subgroup analyses will be conducted for selected efficacy endpoints on the subset of MRD negative subjects (i.e. time to event endpoints).

14.5.6 Safety Analysis

Incident rates for treatment-emergent adverse events, adverse events leading to study drug discontinuation, SAEs and deaths while on study therapy will be summarized.

Treatment-emergent adverse events are defined as follows:

- An adverse event that occurs after treatment start that was not present at the time of treatment start; **OR**
- An adverse event that increases in severity after treatment start if the event was present at the time of treatment start.

Cumulative doses will be calculated for each subject (for elotuzumab, carfilzomib and lenalidomide) in both absolute terms and as a percent of expected cumulative dose (relative dose intensity). Cumulative dose and relative dose intensity will then be summarized for the study arm.

14.5.7 Interim Analysis

No pre-specified interim analyses are planned for this study.

15. STUDY COMPLETION OR TERMINATION

15.1 Completion

The study will be considered complete when one or more of the following conditions is met:

- All subjects have died and/or are withdrawn from the study
- All subjects have discontinued from the study
- The IRB, FDA, LCI DSMC, or Sponsor-Investigator discontinues the study because of safety considerations
- The Sponsor-Investigator defines an administrative or clinical cut-off date

15.2 Termination

The study will be terminated when one or more of the following conditions occur:

- If risk-benefit ratio becomes unacceptable owing to, for example,
 - Safety findings from this study (e.g. SAEs)
 - Results of any interim analysis
 - Results of parallel clinical studies
 - Results of parallel animal studies (e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
 - If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.
- The Sponsor-Investigator has decided to close the trial at any site and at any time

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties.
- All affected institutions must be informed as applicable according to local law.

- In case of a partial study closure, ongoing subjects, including those in follow-up, must be taken care of in an ethical manner.

16. STUDY MANAGEMENT

16.1 IRB Approval

The final study protocol and the final version of the informed consent form(s) must be approved in writing by the Sponsor IRB.

The Sponsor-Investigator is responsible for informing the Sponsor IRB of any amendment to the protocol in accordance with local requirements. The protocol must be re-approved by the IRB annually, as local regulations require.

16.2 Informed Consent

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

16.3 Protocol Adherence

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

16.4 Changes to the Protocol and/or Informed Consent

16.4.1 Amendments to the Protocol

If it is necessary for the study protocol to be amended and/or the informed consent revised, the amendment or a new version of the study protocol (amended protocol) and/or the revised informed consent must be approved by the Sponsor-Investigator, funding company(ies) (if required by the contract(s), the FDA and the Sponsor IRB.

16.4.2 Emergency Modification

The Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior approval from applicable agencies. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the appropriate agencies. Any deviations from the protocol must be explained and documented by the investigator.

16.5 Other Protocol Deviations

If a deviation occurs, the event should be reported to the Sponsor-Investigator via entry in the CTMS no later than 10 business days after awareness.

Protocol deviations that, in the Investigator's judgment, potentially caused harm to participants or others or indicates that the participants or others are at an increased risk of harm, or has adversely impacted data integrity will be reported promptly to the Sponsor-Investigator and IRB per IRB reporting requirements.

NOTE: Planned protocol deviations will be submitted to the FDA for prior approval only if the deviation affects the scientific validity of the study and/or the rights, safety, or welfare of subjects.

16.6 Retention of Records

Essential documentation (e.g. AEs, records of study drug receipt and dispensation), including all IRB correspondence, will be retained for at least 2 years after the investigation is completed. Documentation will be readily available upon request.

16.7 Ethical and Legal Conduct of the Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Investigator abide by GCP guidelines. The study will also be carried out in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6 and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate agencies (e.g. DSMC, IRB, FDA) will be obtained for all participating centers before the start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigators may not modify or alter the procedures described in this protocol.

The Sponsor-Investigator is responsible for the conduct of the clinical trial at the sites in accordance with Title 21 of the CFR and/or the Declaration of Helsinki. The Sponsor-Investigator is responsible for overseeing the treatment of all study subjects. The Sponsor-Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all applicable regulations and guidelines regarding clinical trials both during and after study completion.

The Sponsor-Investigator will be responsible for assuring that all the required data will be collected and properly documented.

16.8 Confidentiality of Records

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

16.9 Compliance with ClinicalTrials.gov

The Sponsor-Investigator is solely responsible for determining whether the trial and its results are subject to the requirements for submission to ClinicalTrials.gov (<http://www.clinicaltrials.gov>).

17. REFERENCES

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18. APPENDICES

18.1 Appendix A: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Reference: Oken MM, Creech RH, Horney RH et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.	

18.2 Appendix B: Cockcroft-Gault Equation

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

18.3 Appendix C: NYHA Classification

Class	Description
I	Subjects with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Subjects with cardiac disease resulting in inability to carry on physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Excerpt from Oxford Textbook of Medicine. Vol. 2, p.2228. Oxford Press. 1997.	